VOLUME 11 • NUMBER 8 • *August 1956*

Geriatrics

DEVOTED TO DISEASES AND PROCESSES OF AGING

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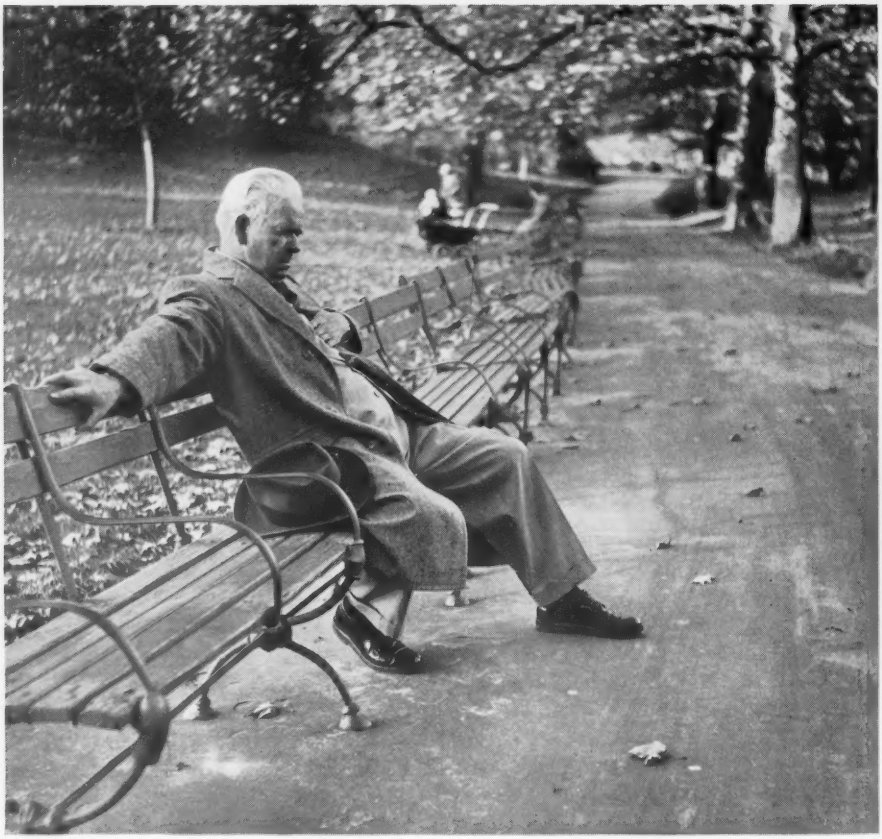

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M.C.: Personal communication.

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Geriatrics

Established 1946

Volume 11
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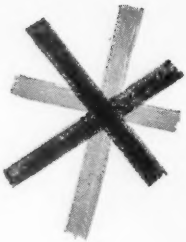

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. . . looking forward

The papers of the September issue will be devoted to one of the most pressing problems of geriatric medicine – *The Care of the Elderly Cancer Patient*. Guest editor for the issue is Charles S. Cameron, M.D., medical and scientific director of the American Cancer Society and an associate editor of *Geriatrics*.

● *Age of Patients in Relation to Radical Cancer Surgery* is not considered as important a factor in evaluating operative risk as it once was, according to Alexander Brunschwig, Memorial Center for Cancer and Allied Diseases, New York City. It is not age per se that constitutes poor surgical risk, but the extent of cardiorenovascular impairment. Persons in advanced age groups are often more fit to withstand the strains of radical surgery than are younger individuals.

● Samuel M. Bluefarb, assistant professor of dermatology, Northwestern University Medical School, stresses the fact that all *Precancerous Dermatoses* do not necessarily become carcinomatous. Less than 50 per cent of the cases of seborrheic keratoses, senile keratoses, leukoplakia, cutaneous horn and arsenical keratoses are apt to become malignant; more than 50 per cent of all cases of kraurosis vulvae, kraurosis penis, and erythroplasia may become malignant. Only Paget's disease, Bowen's disease, and xeroderma pigmentosum carry 100 per cent malignancy.

● Dr. Bluefarb also discusses *Some Nonspecific Cutaneous Lesions Associated with Internal Cancer*, including herpes zoster, exfoliative dermatitis, acanthosis nigricans, and dermatomyositis. Although the exciting cause of herpes zoster is a virus, a predisposing factor may be compression by a malignant tumor. Exfoliative dermatitis is a symptom, rather than a disease entity, and may be secondary to a number of conditions, including carcinoma. Acanthosis nigricans develops almost simultaneously with internal cancer in about 50 per cent of cases.

● Alexander W. Young, Jr., assistant physician to outpatients at New York Hospital, New York City, writing on *Skin Cancer: Diagnosis and Management in the Elderly Patient*, says that treatment must be adapted to the type of lesion, its size, location, degree of malignancy, and age of the patient. It should not be undertaken without specialized knowledge of the underlying clinicopathologic principles of the disorder.

● *The Care of Patients with Advanced Cancer* and afflicted with the ravages of degenerative diseases is one of the great remaining frontiers of medicine, and a challenge to the physician's knowledge and compassion, writes Freddy Homburger, research professor of medicine in the Department of Surgery, Tufts University College of Medicine. The patient may be helped by such available measures as (1) verification of diagnosis even though the cancer is widespread; (2) use of specific chemotherapy for certain neoplasms; (3) use of palliative radiotherapy and surgery; and (4) use of general sustaining measures.

● Although the *Place of Radioactive Isotopes in Cancer Therapy* has not been fully ascertained and their present use is still limited, they provide a new therapeutic tool, especially for palliation of patients with advanced cancer, writes Justin J. Stein, professor of radiology at the University of California School of Medicine, Los Angeles. The isotopes most commonly used for cancer therapy at present are those of phosphorus (P^{32}), iodine (I^{131}), gold (Au^{198}), chromic phosphate ($CrPO_4$), and cobalt.

● Eight years of experience have demonstrated *The Suitability of Home Care for the Cancer Patient*, says I. Rossman, associate attending physician at Montefiore Hospital, New York City. It has been shown that much of the medical care given the patient in the hospital can be made available to the patient in the home. The cancer patient at home is generally more alert and shows more interaction with his environment and his relationship to members of the family is more energetic.

For these and other articles, abstracts, reviews, and special features, read every issue of Geriatrics.

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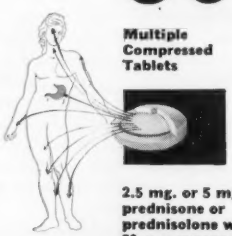

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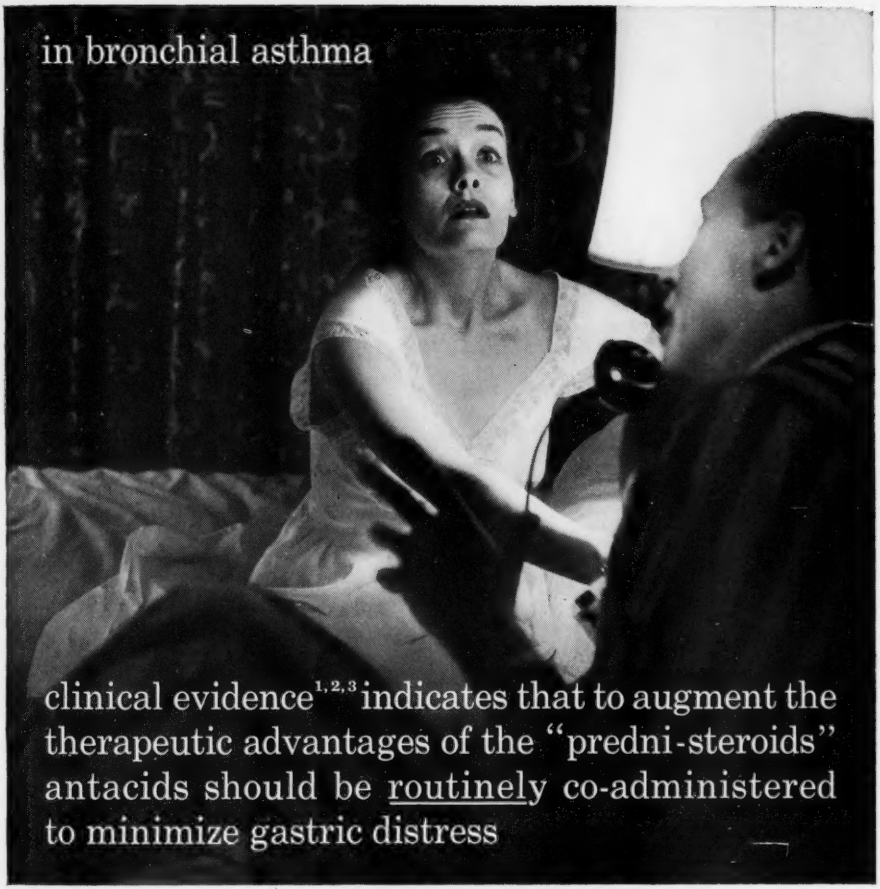
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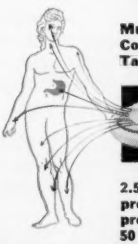

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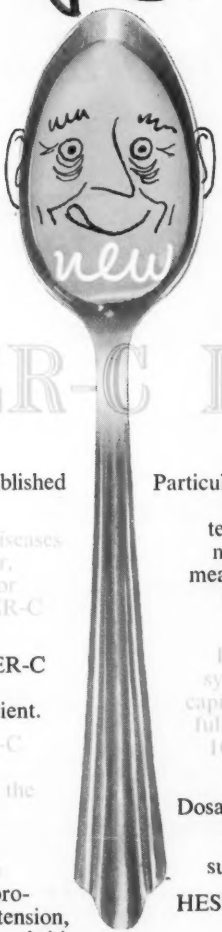

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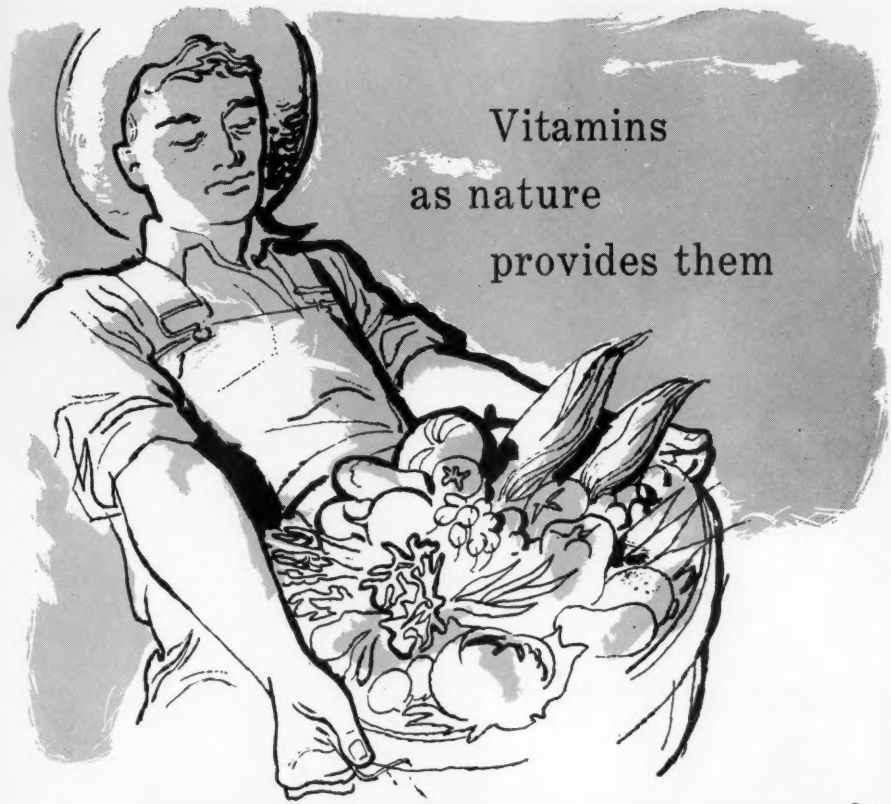

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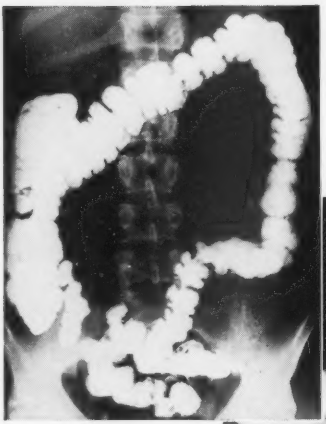

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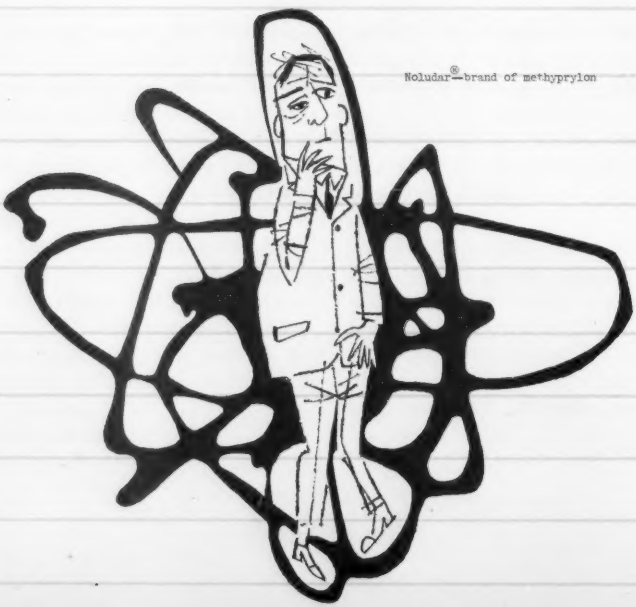
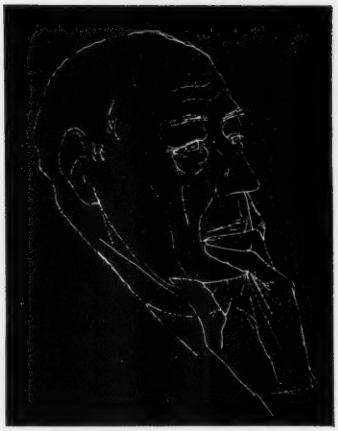


Noludar®—brand of methyprylon



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in older patients...

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When healing is at a standstill in decubitus or varicose ulcers, CHLORESIUM Ointment and Solution encourage the normal repair process. Poor local blood supply, common in peripheral vascular disease, is often at fault—as well as vitamin and protein deficiencies or other factors present in older or bedridden patients.

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(1) Carpenter, E. B.: Clinical Experiences with Chlorophyll Preparations, with Particular Reference to Chronic Osteomyelitis and Chronic Ulcers, Am. J. Surg. *77*:167, 1949. (2) Boehme, E. J.: The Treatment of Chronic Leg Ulcers with Special Reference to Ointment Containing Water-Soluble Chlorophyll, Lahey Clin. Bull. *4*:242, 1946. (3) Smith, L. W.: The Present Status of Topical Chlorophyll Therapy, New York J. Med. *55*:2041 (July 15) 1955.

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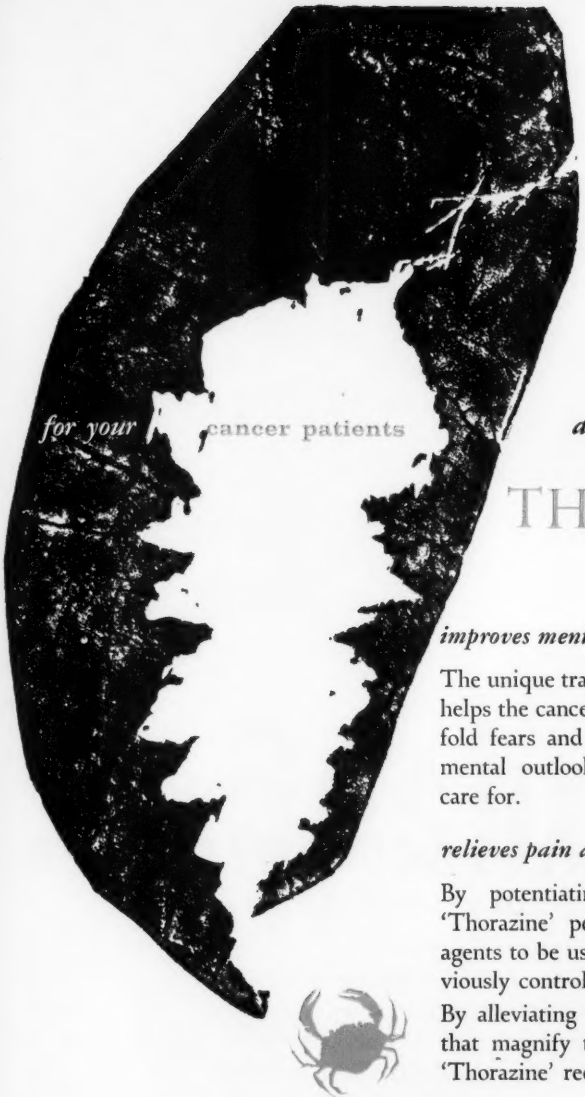

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'Thorazine' promptly controls nausea and vomiting due either to the malignancy or to distressing therapies such as irradiation and nitrogen mustards.

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Ulcer protection that lasts all night:

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Tablets

Each tablet contains:
Methscopolamine bromide ..... 2.5 mg.

Average dosage (ulcer):
One tablet one-half hour before meals, and 1 to 2 tablets at bedtime.

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Each 5 cc. (approx. 1 tsp.) contains:
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Each cc. contains:
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The physically sick patient faces two stresses—the sickness and the anxiety that it brings.[1] All too often, the anxiety is a threat to the patient's progress. It may intensify symptoms, give uncertainty to therapy, and impair rapport.

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Supplied: Tablets, 400 mg., bottles of 50.
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1. Braceland, F.J.: Texas State J. Med. 51:287 (June) 1955.
2. Lemere, F.: Northwest Med. 54:1098 (Oct.) 1955.

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Meprobamate
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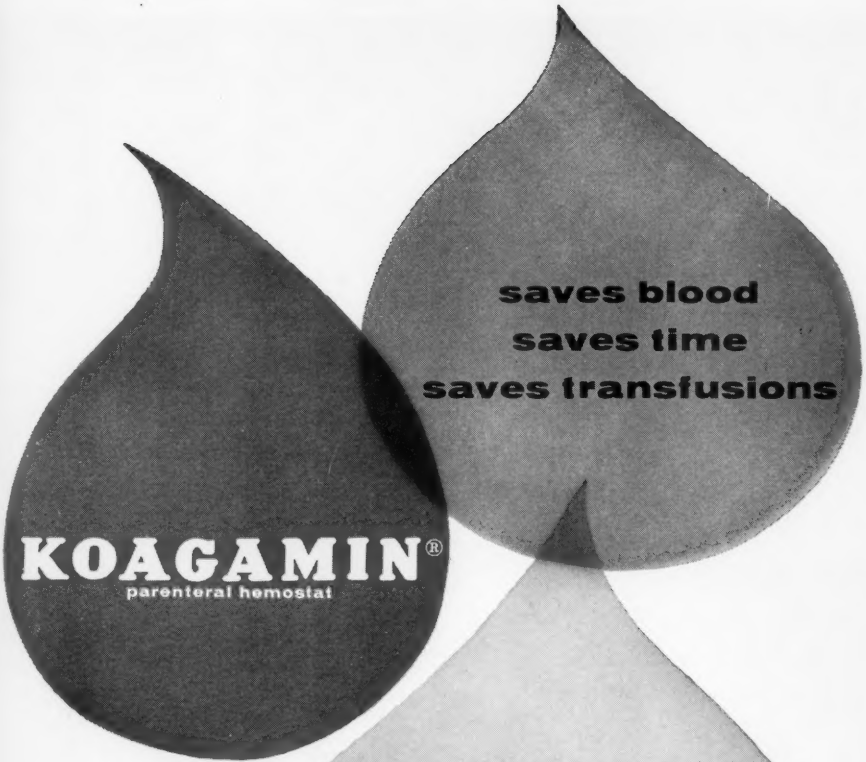
anti-anxiety factor with muscle-relaxing action



in surgery—Given prophylactically in 567 surgical cases, a single injection of KOAGAMIN was found "...to reduce blood loss and to facilitate surgical procedures...often obviate[s] the use of transfusion...."*

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*Joseph, M.: Am. J. Surg. *87*:905, 1954.

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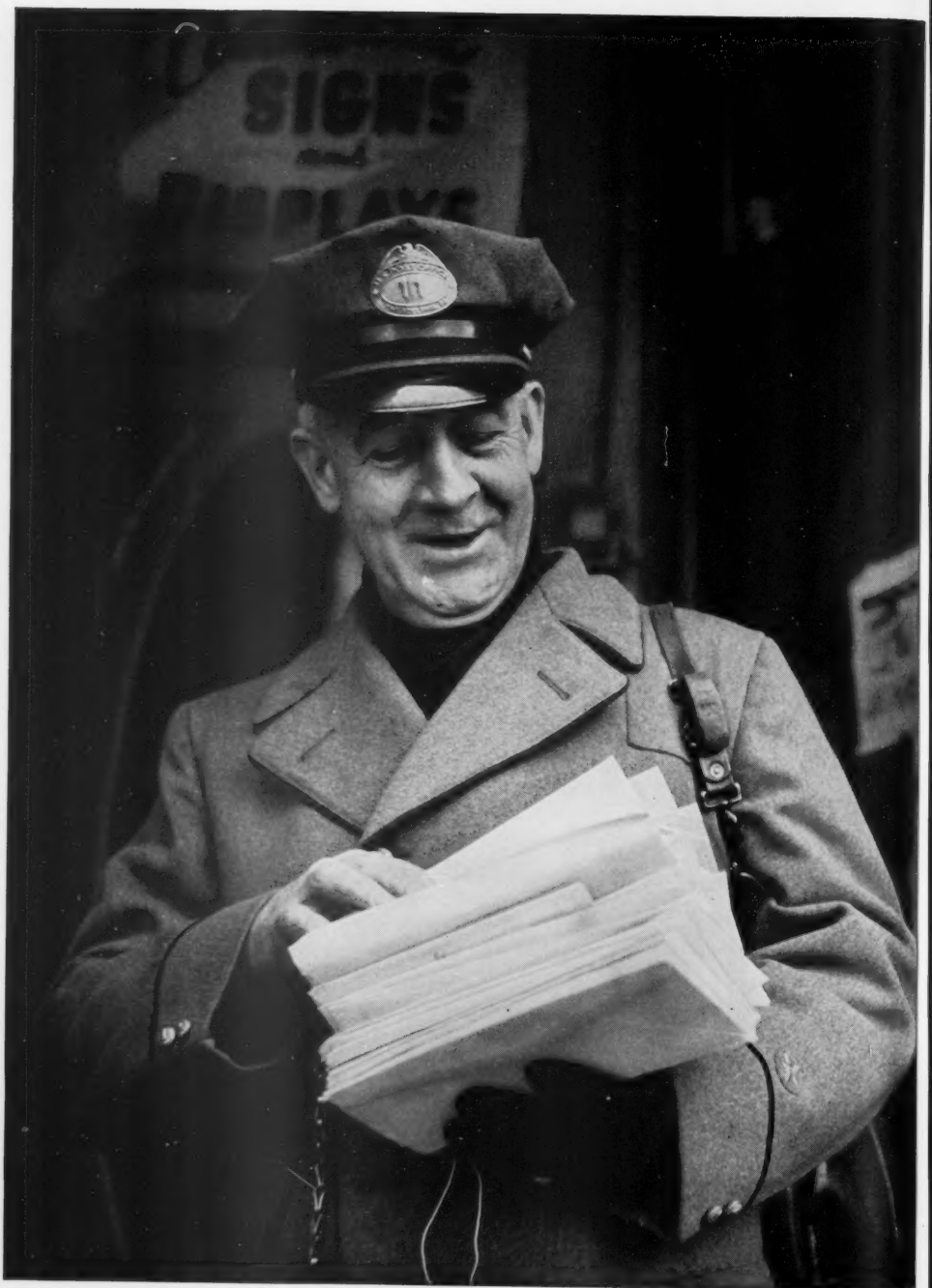
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"Neither rain, nor snow, nor advancing years shall stay this courier!"

For persons past forty, good health is usually a source of great pride and satisfaction. Each succeeding year seems to heighten their delight and appreciation. To help these "senior citizens" maintain their vigor, prescribe GEVRAL, a comprehensive geriatric diet supplement that provides 14 vitamins, 11 minerals, and Purified Intrinsic Factor Concentrate—all in one convenient, *dry-filled* capsule.

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GERIATRIC VITAMIN-MINERAL SUPPLEMENT LEDERLE

Each GEVRAL Capsule contains:

Vitamin A	5000 U.S.P. Units	Rutin	25 mg.
Vitamin D	500 U.S.P. Units	Purified Intrinsic Factor Concentrate	0.5 mg.
Vitamin B_{12}	1 mcgm.	Iron (as $FeSO_4$)	10 mg.
Thiamine Mononitrate (B_1)	5 mg.	Iodine (as KI)	0.5 mg.
Riboflavin (B_2)	5 mg.	Calcium (as $CaHPO_4$)	145 mg.
Niacinamide	15 mg.	Phosphorus (as $CaHPO_4$)	110 mg.
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Pyridoxine HCl (B_6)	0.5 mg.	Copper (as CuO)	1 mg.
Ca Pantothenate	5 mg.	Fluorine (as CaF_2)	0.1 mg.
Choline Dihydrogen Citrate	100 mg.	Manganese (as MnO_2)	1 mg.
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Ascorbic Acid (C)	50 mg.	Potassium (as K_2SO_4)	5 mg.
Vitamin E (as tocopheryl acetates)	10 I.U.	Zinc (as ZnO)	0.5 mg.

dry-filled sealed capsules

for more rapid and complete absorption, freedom from aftertaste. A Lederle exclusive!

Other Lederle geriatric products include: *GEVRABON** Vitamin-Mineral Supplement Liquid with a wine flavor; *GEVRAL** Protein Vitamin-Mineral-Protein Supplement Powder; and *GEVRINE** Vitamin-Mineral-Hormone Capsules.

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For Constipation in
Aged Cardiac Patients

Dear Doctor:

Many aged cardiac patients suffer from constipation and take laxatives regularly. "The diminished appetite caused by cardiac drugs, the purges which reduce the vitamins, minerals, and electrolytes from the body, are condemning these persons to inevitable deterioration." [1]

"Attention should be paid to patient's bowel movements, which should be regulated without resorting to cathartics." [1] For these patients, Malt Soup Extract provides a safe, effective dietary means of overcoming constipation.

Send for folder
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1. Monat, H. A.: Geriatrics 10: 581, 1955.

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BORCHERDT COMPANY

GOOD FOR GRANDMA, TOO!

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MALT SOUP Extract*

A New Dietary Management for

CONSTIPATED ELDERLY

A bowel content modifier that softens dry, hard stools by dietary means without side effects.[1] Acts by promoting an abundant fermentative bacteria in the colon, thus producing soft, easily evacuated stools. Retards growth of putrefactive organisms. By maintaining a favorable intestinal flora, Malt Soup Extract provides *corrective therapy for the colon, too!*

DOSE: 2 tablespoonfuls b.i.d. until stools are soft (may take several days), then 1 or 2 Tbs. at bedtime.

*Specially processed malt extract neutralized with potassium carbonate. In 8 oz. and 16 oz. bottles.

1. Cass, L. J. and Frederik, W. S.: Malt Soup Extract as a Bowel Content Modifier in Geriatric Constipation. Journal-Lancet, 73:414 (Oct.) 1953.

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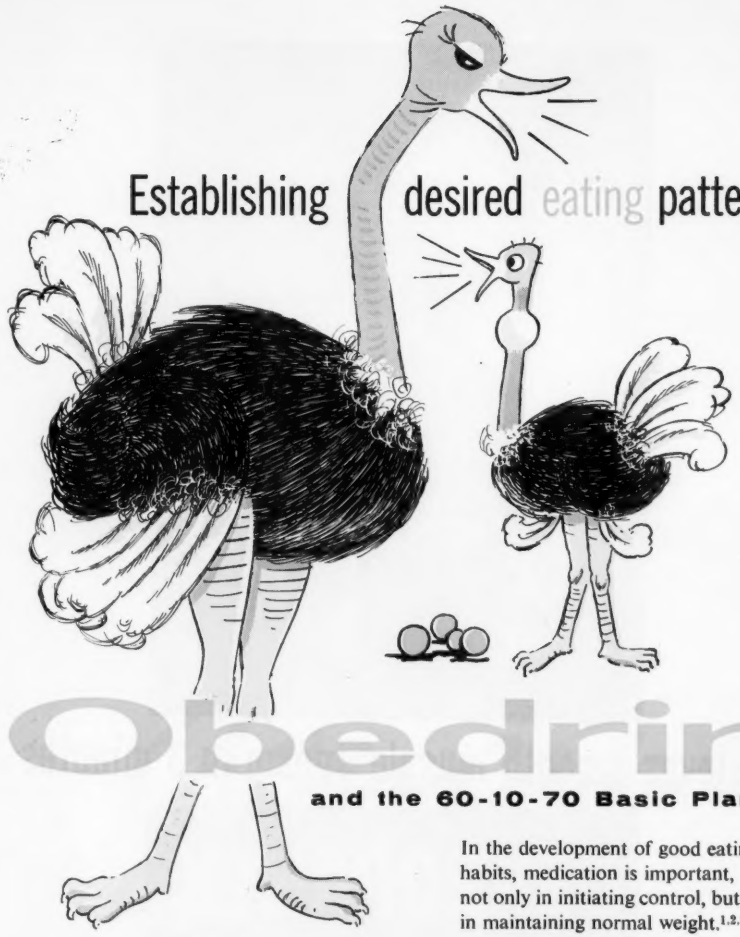

Establishing desired eating patterns

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and the 60-10-70 Basic Plan

In the development of good eating habits, medication is important, not only in initiating control, but also in maintaining normal weight.[1,2,3]

Obedrin contains:

- Methamphetamine for its anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B_1 and B_2 plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Since Obedrin contains no artificial bulk, the hazards of impaction are avoided. The 60-10-70 Basic Plan provides for a balanced food intake, with sufficient protein and roughage.

Formula

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine HCl 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).

2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).

3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

Write for 60-10-70 Menu pads, weight charts, and samples of Obedrin.

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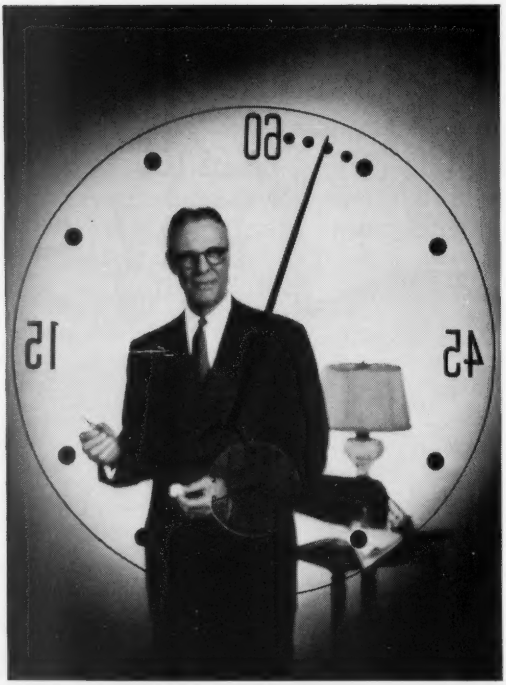

Relieves smooth muscle spasm in 3 minutes[1]

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When you relieve spasm with DEPROPANEX, patients cooperate more readily during urological procedures. In renal and ureteral colic, relief of pain may follow within three minutes of an injection of DEPROPANEX. In biliary colic, too, DEPROPANEX is markedly effective. And in abdominal surgery, DEPROPANEX has been effective in paralytic ileus.

Reference: 1. South M. J. 31:233, 1938.

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IN DIABETES...

greater security against vascular complications

Increased threat of vascular complications in diabetic patients can result from recurring episodes of inadequate control; at such times amino acids are "wasted" by de-amination in the liver and normal dietary security against lipotropic deficiency fades.

TRADE MARK

Gericaps

(Sherman Lipotropic Capsule) **One capsule t.i.d.**

Gericaps contain the true lipotropics, choline and inositol, which are unaffected by de-amination in the liver. Three capsules daily provide the equivalent of 3 Gm. choline dihydrogen citrate.

This dose also provides 60 mg. rutin and 37.5 mg. ascorbic acid to maintain or improve capillary integrity, as well as 3000 units vitamin A, 3 mg. thiamine hydrochloride, 3 mg. riboflavin, 12 mg. niacinamide, 0.75 mg. pyridoxine hydrochloride, and 3 mg. calcium pantothenate.

SEND FOR comprehensive review:
"Prevention of Vascular Complications of Diabetes"

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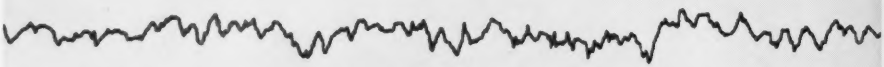
WHAT IS THE DIFFERENCE BETWEEN A TRANQUILIZER AND A SEDATIVE?

Comparison of the effect of Raudixin (tranquilizer) and a barbiturate (sedative) on the cortical electroencephalogram

No drug.



After Raudixin. E. E. G. not altered.

After barbiturate. Typical "spindling" effect.

Because barbiturates and other sedatives depress the cerebral cortex, the sedation achieved is accompanied by a reduction in mental alertness.

Raudixin acts in the area of the midbrain and diencephalon, and does not depress the cerebral cortex. Consequently, the tranquilizing (ataractic) effect achieved is generally free of loss of alertness.

RAUDIXIN

Squibb Whole Root Rauwolfia Serpentina

DOSAGE: 100 mg. b.i.d. initially; may be adjusted within a range of 50 mg. to 500 mg. daily. Most patients can be adequately maintained on 100 mg. to 200 mg. per day.

SUPPLY: 50 mg. and 100 mg. tablets; bottles of 100, 1000 and 5000.

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Squibb Quality—the Priceless Ingredient

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(ETHCHLORVYNOL, ABBOTT)

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PLACIDYL enables the physician to *induce* sleep instead of *imposing* it. Nonbarbiturate. No initial excitation or respiratory depression. A halogenated carbinol, sold under no other trade name. Abbott

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scaling scalp?

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Selsun®

relieves seborrheic dermatitis of the scalp and dandruff –quickly, easily, economically.

Just one or two Selsun applications relieve itching, burning scalps. Scaling is completely controlled in 81-87% of seborrheic dermatitis, 92-95% of dandruff cases. And relief lasts — up to four weeks — with each pleasant application. Selsun Suspension is sold only on prescription, in 4-fluidounce bottles with directions.

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hypnotic

prompt action

rapid elimination

clear-headed awakening

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Each contains 0.03 Gm (½ grain) of Alurate per teaspoonful (4 cc)
in a palatable vehicle. Alurate®—brand of aprobarbital

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HOW OLD IS OLD?

"The really old people are those 10 years older than myself."[1]

"In the lay mind, anyone past 60 is ready for the discard . . ."[2]

". . . there are only three principal phases in the span of life: infancy, adolescence and senescence."[3]

"One finds alert, interesting, active folks in the 80's and, on the other hand, there are people in the 20's and 30's who have all the characteristics of old age."[4]

THE REAL QUESTION

To the physician on the firing line of daily practice, the question of "how old is old?" seems academic. To him, a more valid question is "How can I allay the effects of the aging process?"

FIVE PROBLEMS IN AGING

The answer, according to most authorities, is manifold, for five treatable problems seem to predominate. One, obviously, is gonadal hormone decline. Another is mild anemia. A third is the decreased production of gastric and digestive enzymes. Mineral-vitamin deficiency is the fourth. And the fifth – perhaps most important – is inadequate high-quality protein intake.

THERAPY FOR AGING

Judging from this confused clinical picture of aging, therapy for the problem would appear difficult. However, most physicians agree that a product which could correct most or all of these five commonest problems would remove past obstacles to satisfactory response. Such a product would, essentially, be true "preventive geriatrics."

NEOBON'S COMPREHENSIVE FORMULA

NEOBON®, a product of Roerig research, is a blended combination of the five most commonly indicated factors for prevention or treatment of the nonacute conditions of aging. Each soft, soluble capsule provides:

Non-stimulatory gonadal hormone replacement

balanced hematinic component

digestant enzyme replacement

specially formulated mineral-vitamin combination

new lysine, for protein improvement*

* Protein deficiency among the aging apparently stems from their excessive intake of white-flour foods which furnish incomplete protein of low biologic value. White bread protein, for example, has been shown by nutrition studies in animals[5] to be deficient only in the amino acid, lysine. In human subjects metabolic determinations indicate that the addition of supplemental lysine to a basal white-flour protein diet can convert a negative nitrogen balance into a positive one.[6]

A WORD ABOUT SYMPTOMATOLOGY

In spite of jokes to the contrary, the patient who states in the professional office that "old age is creeping up" is a rare bird indeed.

Seldom is old age the presenting complaint. Thus the physician, after correcting the specific complaints, must re-evaluate the whole person to judge his candidacy for "preventive geriatrics." Such people have much to gain from NEOBON therapy. The rewards are fuller, more active, more pleasurable years for patients past 40. The daily dose (3 capsules) of NEOBON provides:

L-lysine	150 mg.
Methyltestosterone	3 mg.
Ethinyl Estradiol	0.018 mg.
Pancreatic Substance***	150 mg.
Glutamic Acid	90 mg.
Rutin	15 mg.
Vitamin A (Palmitate)	6,000 U.S.P. Units
Vitamin D (Irradiated Ergosterol)	600 U.S.P. Units
Vitamin E (as Tocopheryl Acetate)	15 I.U.
Calcium Pantothenate	15 mg.
Thiamine Mononitrate (Vitamin B_1)	1.5 mg.
Riboflavin (Vitamin B_2)	1.5 mg.
Pyridoxine Hydrochloride (Vitamin B_6)	1.5 mg.
Niacinamide	150 mg.
Ascorbic Acid (Vitamin C)	150 mg.
Vitamin B_{12} (Oral Concentrate)	3 mcg.
Folic Acid	0.3 mg.
Liver-Stomach Substance**	300 mg.
Iron (from Ferrous Gluconate)	10.2 mg.
Cobalt (from Cobaltous Sulfate)	0.1 mg.
Molybdenum (from Sodium Molybdate)	2 mg.
Copper (from Cupric Sulfate)	1 mg.
Manganese (from Manganous Sulfate)	1 mg.
Magnesium (from Magnesium Sulfate)	6 mg.
Iodine (from Potassium Iodide)	0.15 mg.
Potassium (from Potassium Sulfate)	5 mg.
Zinc (from Zinc Sulfate)	1.2 mg.

**Enzymatically active defatted material obtained from 1,500 mg. whole fresh liver and stomach.

***Enzymatically active defatted material obtained from 750 mg. of whole fresh pancreas.

Dosage: 3 capsules daily, with meals.

Supplied: Bottles of 60 capsules, prescription only.

NEW NEOBON® LIQUID

A GERIATRIC TONIC

Now also available for your consideration is NEOBON LIQUID, which provides hematinic action, improved carbohydrate and protein utilization, gonadal and thyroid hormone supplementation and a mild antidepressant action.

The pleasant tasting liquid is especially indicated when a combined attack against nutritional, physiological and mental depression is indicated. Each teaspoonful (5 cc.) of pleasant-tasting NEOBON LIQUID contains:

Ferrous Gluconate	30 mg.
Ascorbic Acid	50 mg.
d-Amphetamine Sulfate	0.5 mg.
Folic Acid	167 mcg.
Vitamin B_{12}	2.5 mcg.
l-Thyroxine	0.1 mg.
Ethinyl Estradiol	1 mcg.
Methyltestosterone	1 mg.
Liver Fraction I	25 mg.
Ethyl Alcohol	0.5 cc.

Dosage: One teaspoonful twice daily before meals, or as required.

Supplied: In 16 fluid ounce bottles, prescription only.

Bibliography

1. Anonymous. 2. Rosenthal, P.: Geriatrics 10:382 (August) 1955. 3. Lansing, A. I.: Symposium on Problems of Gerontology, National Symposium Series No. 9 (August) 1954. 4. Mason-Hohl, E.: Quoted in W. Va. Med. J. 51:16 (January) 1955. 5. Rosenberg, H. R., et al.: Arch. Biochem. and Biophys. 49:263, 1954. 6. Bricker, M., Mitchell, H. H. and Kinsman, G. M.: J. Nutrition 30:269, 1945. 7. Masters, W. H. and Ballew, J. W.: Geriatrics 10:1, 1 (January) 1955.

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because a diuretic
should be able to control
any degree of failure

PATIENTS IN FAILURE NEED AN ORGANOMERCURIAL

Certain diuretics are apt to mask the gradual onset of severe failure because they are effective only in the milder ambulatory cardiacs. The recurrent accumulation of fluid permitted by intermittent or arbitrarily limited dosage must eventually progress to more severe decompensation.

Because they can control *any* grade of failure, the organomercurials improve prognosis and prolong life.

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NEOHYDRIN®

BRAND OF CHLORMERODRIN (18.3 MG. OF 3-CHLOROMERCURI-2-METHOXY-PROPYLUREA EQUIVALENT TO 10 MG. OF NON-IONIC MERCURY IN EACH TABLET)

a standard for initial control of severe failure

MERCUHYDRIN® SODIUM

BRAND OF MERALLURIDE INJECTION

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LAKESIDE

Volume 11, Number 8 Geriatrics

Pathogenesis and treatment of senile osteoporosis

MARC MOLDAWER, M.D.
BOSTON, MASSACHUSETTS

Osteoporosis results when stimuli to bone production fail to balance bone resorption. Of the multiple factors involved in such failure, the diminution in anabolic hormones with age can be controlled by replacement therapy with sex hormones, with arrest and partial reversal of the process. Understanding of the other factors can prevent mistaken and sometimes dangerous therapeutic approaches. Immobilization of the osteoporotic patient is to be avoided.

◆ Although osteoporosis is defined as a disorder of the protein matrix of bone, the term is often used interchangeably with the term osteomalacia. The confusion is not merely semantic, but indicates a reluctance to accept the evidence that osteoporosis is not primarily a derangement of calcium metabolism. Whether the disturbance is primarily one of protein or of calcium metabolism has important consequences for treatment and for further research. It may be well, therefore, to review this evidence before considering the clinical aspects of senile osteoporosis.

Normal Bone Metabolism

Normal bone is in a state of dynamic equilibrium. Bone is constantly being destroyed at some, and formed at other trabecular surfaces, in equal amounts. The normal state of undersaturation of body fluids with respect to calcium and phosphorus leads to continual resorption of bone calcium and phosphorus into the blood. The ratio of the crystalline calcium-phosphorus-carbonate apatite to the protein matrix is probably constant. When phosphorus and calcium are withdrawn from bone into the body fluids, the matrix in which they were deposited disappears simultaneously. Viewed in this way, bone resorption is basically a passive process. In areas where bone salt is being resorbed, osteoclasts can be seen, which appear to be the active agents of matrix dissolution.

MARC MOLDAWER, *who holds fellowships from the United States Public Health Service and Harvard University, is currently engaged in graduate study in the Department of Biochemistry at the University of Cambridge, England.*

Resorption of bone mineral and diminution of matrix stimulate the active process of bone production. When there is gross weakening of bone, or where stresses and strains on bone are intense, there is normally very active bone production. The constantly occurring resorption of bone, by weakening it and placing excess stresses and strains on it, is thought to be the agent of stimulation of new bone formation. The mechanisms of this stimulation are not clear. Unlike the simultaneity of bone crystal resorption and matrix destruction, production seems to be a stepwise process: matrix is formed, into which the calcium salts are subsequently precipitated. Normally there is little time difference in these steps, which appear to be almost simultaneous. In osteomalacia, gross undersaturation of the body fluids with respect to calcium and phosphorus both increases resorption and prevents precipitation, so that large amounts of uncalcified matrix can be seen. Uncalcified, or acalcified matrix, then, may be evident under certain conditions, but decalcified matrix has not been described. At the trabecular surfaces where matrix is being formed, osteoblasts are evident. These produce the bone matrix and the enzyme alkaline phosphatase, one function of which is to increase local concentrations of inorganic phosphorus and thus permit precipitation of bone salt from the normally undersaturated body fluids.

It is probable that the rate of resorption varies from area to area in the skeleton. The over-all rate varies from time to time, depending on changes in the serum levels of calcium and phosphorus.

Bone resorption is itself a means of maintaining constant body fluid levels of calcium and phosphorus. Control is also effected by variable absorption and reexcretion of calcium into the gastrointestinal tract and by a renal threshold for calcium. The parathyroid hormone, by altering the renal threshold for phosphorus, further regulates blood levels.

Histology and Pathogenesis of Osteoporosis

The surfaces of osteoporotic bone trabeculae are histologically very similar to those of normal bone. Osteoblasts are seen at some surfaces, osteoclasts at others. There are neither areas of decalcified matrix in the regions of osteoclastic activity, nor unusual areas of uncalcified matrix where the osteoblasts are congregated. The difference from normal bone is that the trabeculae are thinner and fewer than normal. As far as is now known, osteoporotic bone substance does not differ chemically from normal bone: the matrix collagen has not been shown to be abnormal, nor has the bone salt, and the ratio of one to the other is probably as in normal bone. There may be a relative and absolute decrease in the number of osteoblasts, but this cannot be ascertained histologically.

In order for the trabeculae to have become thinner, one of two things must have occurred: bone destruction must have been greater than normal, or bone production must have been less than normal. Since "normal" would be that variable level by which equilibrium is maintained, it might be preferable to say that bone destruction has been greater than bone production, or bone production less than bone destruction. Since the process of resorption is thought to be passive, dependent on the state of the body fluids, one might expect some abnormality of calcium metabolism. In osteoporosis, however, the serum calcium and phosphorus values are normal, and therefore there would be no impetus to an excessive breakdown of bone. It has been suggested that a very slight increase in the degree of undersaturation of the blood, not detectable by routine calcium and phosphorus determinations, and not so great as to prevent precipitation of bone salts into newly formed matrix, might be responsible. This does not seem

tenable, for, since there is normally a considerable reserve of osteoblastic function, bone matrix production would be expected to keep pace with the increased destruction, as it does in true osteomalacia.

There is no other evidence of a primary error in calcium metabolism. Although some patients with osteoporosis may have had a diet poor in calcium and phosphorus or may have absorption difficulties, balance studies have repeatedly shown negative balances to be present despite adequate intakes and absorption, and that further increases in intake and absorption do not alter the balance. No abnormality of the parathyroid glands has been demonstrated in patients with osteoporosis. The glands appear to be normal histologically, rather than hypertrophic as in osteomalacia.

The failure to find any error in calcium metabolism or any factor actively destroying bone, therefore shifts attention to a decrease in bone matrix production as the primary problem. It is here that current theory localizes the difficulty: bone production is insufficient to balance bone destruction; the matrix which is formed is normal and normally calcified, and there is just too little of it.

Etiology of Senile Osteoporosis

No single cause of senile osteoporosis is apparent. Many factors have been considered, each of which, of itself, may produce osteoporosis.

OSTEOPOROSIS OF DISUSE

As already mentioned, stress and strain appear to be a major stimulus to bone production. When the body or a part of it is immobilized, bone resorption continues, but bone production is markedly reduced and osteoporosis results. This can readily be seen following immobilization of a fractured extremity in a cast, but occurs under any condition where inactivity has been extensive or prolonged. In old age, a general decrease in physical activity is undoubtedly a factor in the production of osteoporosis.

PROTEIN DEFICIENCY

In starvation or other conditions of protein deficiency, osteoporosis may result. The frequency with which the diet of elderly people is deficient in protein suggests this as a possible cause, but it is certainly not the sole cause. Dietary histories of elderly patients with osteoporosis frequently reveal quite adequate intakes, and studies may show adequate absorption, while there appears to be inadequate utilization in the construction of bone matrix. This is clearly seen in studies where high protein diets have been given without modifying the nitrogen or calcium balance. The possibility of a specific error in protein metabolism cannot be excluded, but none has thus far been demonstrated.

VITAMINS AND MINERALS

That senile osteoporosis is not caused by deficiency nor by poor absorption of calcium and phosphorus has already been mentioned. Similarly, there is no evidence that it is due to a deficiency of other minerals or of vitamins, with the exception of true scurvy, in which osteoporosis is sometimes seen. Vitamin B_{12} deficiency and trace-metal deficiencies have been suggested, but there is as yet no evidence that these play any role in the etiology of senile osteoporosis.

ENDOCRINE DISTURBANCES

Cushing's disease, acromegaly, and hyperthyroidism may each be associated with severe osteoporosis. In Cushing's disease, an excess of the anti-anabolic adrenal S-hormone prevents adequate synthesis of bone matrix protein, as it does that of muscle and other tissue proteins. The relation of excessive growth hormone and thyroid hormone to osteo-

porosis is less clear. Both of these hormones are normally anabolic, and it is possible that osteoporosis results only when there is a deficiency of available protein relative to increased metabolism induced by excess of these hormones.

In the postmenopausal state, there is both an absolute and a relative deficiency of anabolic hormones, and osteoporosis would therefore be anticipated. Estrogens, which are anabolic, almost entirely disappear; the anabolic adrenal N-hormone probably diminishes; and, although the anti-anabolic S-hormone may diminish, it is relatively preponderant. In addition, there is the possibility that growth hormone is increased after the menopause, adding an increased rate of metabolism to the preponderance of anti-anabolic hormones. The differing rates of hormonal changes in different persons may account for the variable degrees of osteoporosis in individuals of similar ages. That they occur in all persons probably accounts for the universality and "physiologic" nature of senile osteoporosis. The shift to anti-anabolism is earlier and more acute in the female, which probably explains the increased incidence of pathologic osteoporosis in women. We would consider the term postmenopausal osteoporosis to be interchangeable with the term senile osteoporosis.

Thus, all of the individual causes of osteoporosis—decreased activity, possibly undetected dietary insufficiencies, and a hormonal balance favoring anti-anabolism—may play a role in senile osteoporosis. Arteriosclerosis, with a reduction in blood supply to bone, probably also plays a role. In addition, the condition of "ideopathic osteoporosis" found in some otherwise normal adults whose activity, blood supply, diet, and hormonal balance are all unremarkable, suggests that other, as yet undelineated factors require consideration, as does the observation that osteoblastic failure is not absolute in any form of osteoporosis.

Clinical Aspects of Senile Osteoporosis

The characteristic symptom of senile osteoporosis is back pain, more often of the lower thoracic and upper lumbar regions than elsewhere. The pain may be acute or gradually progressive, and may be localized or diffuse. The classical description is that, after several years of mild back-consciousness, with a heavy or dragging feeling, an acute episode occurs following a mild trauma. Yet there are numerous variations and exceptions to this pattern. The back pain may be accompanied by radiating pains downward to the thighs, laterally to the abdomen, and upward along the spine. Occasionally referred pain may be more pronounced than pain in the back itself.

Tenderness over a spinous process or lateral to the spine may be present, particularly after compression of a vertebra. Limitation of movement, caused chiefly by unwillingness to move because movement increases pain, may be prominent, but neither it nor tenderness may be present. Rarely does nerve compression result in paralyses or sensory changes. Multiple fractures may result in kyphosis, in shortening of the trunk with approximation of the costal margins to the iliac crest, and the appearance of a transverse fold of flesh across the upper abdomen.

Back symptomatology in senile osteoporosis is emphasized because it is so often the only symptom. In elderly people, osteoporosis is also the underlying cause of the many fractures of other bones following mild trauma.

Radiological Aspects of Senile Osteoporosis

There is frequently a discrepancy between symptom and radiologic evidence of osteoporosis. Severe osteoporosis with multiple fractures may be an incidental radiologic finding. In a survey of 136 occupants of a home for the aged, who were without present or prior symptom

referable to the back, it was found that 35 – 29 per cent of the women and 11 per cent of the men – had from one to seven compression fractures of the vertebrae attributable to osteoporosis.[1] The reverse of this situation is not uncommon, and severe symptoms may be present when radiologic evidence is slight. Whether osteoporosis per se, without structural deformity, produces symptoms has been much debated. In general, one is reluctant to diagnose osteoporosis as the cause of symptoms without radiologic or other evidence of structural change, although we, as others, have observed elderly patients whose symptoms began prior to radiologic evidence of fractured or deformed vertebrae.

Whether the frequency with which symptoms occur in the low back is caused by a more pronounced failure of osteoblastic activity in this region or to mechanical factors peculiar to this area is impossible to say. It is, however, the part of the skeleton where osteoporosis is most readily demonstrated radiologically, whether or not there are symptoms. Although Kesson,[2] in surveying the senile skeleton, believed the condition could first be demonstrated in the feet, then in the hands and spine, others[3,4] find that the spine is the most common and often the only part of the skeleton in which senile osteoporosis can definitely be seen radiologically.

The prominence of radiologic changes in the middle and low back may be more apparent than real, because of technical considerations. The trabeculae of the lower spine are, however, somewhat less dense in the normal adult than are those of the upper vertebrae,[5] so that less loss of substance, coupled with increased mechanical stress, may lead to earlier structural and radiologic changes in this region.

Without structural change, osteoporosis is not easy to diagnose roentgenologically; even with such changes a radiologic diagnosis is not definitive, as will be discussed later. Those conditions which are seen most often are the so-called "cod-fish," biconcave vertebrae and collapsed vertebrae, which may be present with or without biconcavity of others, and which most commonly appear to be wedge-shaped, with the narrow edge anterior on a lateral film (figure 1). Osteoporotic bone may appear less dense than normal, although the margins may by contrast appear to be more prominent. Transverse and longi-

FIG. 1. *Radiograph of the lumbar spine of a 60-year-old woman with senile osteoporosis. Note the biconcavity of the vertebrae, their homogeneous appearance with absence of trabecular pattern, and the partial collapse of the first lumbar vertebra.*

FIG. 11. *Radiograph of the lumbar spine of a 74-year-old man whose only complaint was of back pain. Physical examination revealed only tenderness in the lower back. The postmortem diagnosis was carcinoma of the lung with metastases to the first and third lumbar vertebrae. Note the similarity of the radiograph to figure 1. Although senile osteoporosis was present, symptoms were almost certainly caused by metastatic disease, although it could not be discerned from the radiologic examination.*

tudinal markings may no longer be present, the transverse tending to disappear before the longitudinal both radiologically and pathologically.[6] The difficulty in diagnosing osteoporosis on such evidence alone, without accompanying deformity, is that a ground-glass appearance, caused by faulty radiologic technic, may be observed on films of normal bone.

With structural changes in the bones, the intervertebral disks will also be deformed. They may be expanded in their centers, the compressed nucleus pulposus expanding into the depressed vertebrae, but since senile disks become less elastic, the disk may be narrowed. Disk herniation is not uncommon.

Laboratory Examinations

The serum calcium and phosphorus are normal in senile osteoporosis, as has already been mentioned. The serum alkaline phosphatase level is usually normal but, following recent fracture of a vertebra or other bone, may be elevated. Since osteoporosis is a state in which less bone is formed than is destroyed, and since calcium that is not structurally associated with bone matrix is not stored in bone, one would expect the urine calcium to be higher than normal. This is often the case. As osteoporosis develops slowly in the aging skeleton, with only a slight discrepancy between resorption and production of bone, and since the range of normal urinary calcium values is moderately broad, the hypercalciuria is often not marked and may not be evident at the time when measurements are made. Among routine laboratory studies, no other abnormalities are noted. Routine urinalysis, blood counts, sedimentation rate, serum protein level, and the ratio of serum albumin to serum globulin are not abnormal in uncomplicated senile osteoporosis.

Differential Diagnosis

The signs, symptoms, radiologic appearance, and laboratory data are not distinctive in senile osteoporosis, and the diagnosis must be made by exclusion of other causes of back pain. Although osteoporosis is a common cause of pathologic fracture, and its most common benign cause, it is so less often in hospital practice than is metastatic malignancy. Of 660 consecutive patients presenting pathologic fractures, Ghormley, Sutherland, and Pollack reported that the di-

agnosis in 278 was metastatic malignancy.[7] Primary malignancy was found in 106 instances, while of 269 benign lesions, the diagnosis was senile osteoporosis in 92. The majority of the osteoporotic fractures were vertebral.

METASTATIC MALIGNANCY AND MULTIPLE MYELOMA

In some instances, metastatic malignancy or multiple myeloma may diffusely infiltrate the vertebral column (figure II). If back pain is the only symptom found by a complete history, if physical examination suggests no other difficulty, if spinal radiographs show only diffuse rarefaction with or without fracture, if the serum calcium phosphorus and alkaline phosphatase are normal, and if the urine calcium is elevated as expected in both osteoclastic metastases and in osteoporosis, the correct diagnosis may be impossible until further signs or symptoms supervene. Fortunately, such confusion is not common, but Bachman's study of 31 spines with metastatic lesions, in which the lesions were demonstrable radiologically in only 15, emphasizes the danger.[8] Determination of the sedimentation rate may be helpful, since it is normal in osteoporosis but often elevated in metastatic disease and multiple myeloma. Similarly, an abnormality of the serum proteins may be a clue to the nature of the lesion. If Bence-Jones protein is present in the urine, the diagnosis is multiple myeloma.

OSTEOMALACIA

This condition, although very different pathologically, may appear very similar to osteoporosis by radiologic examination. Bone density is diminished in both, and trabeculae are less evident, but the distribution is quite different. By the time it has become symptomatic, osteomalacia is often evident in the entire skeleton, including the skull, which by roentgenogram almost never appears to be involved in osteoporosis. The finding of pseudofractures by radiographic examination is diagnostic of osteomalacia. Dental films of patients with osteomalacia may show absence of the lamina dura, which does not disappear in osteoporosis. Back pain as the single symptom of osteomalacia would be quite unusual. There is, more often, aching of the extremities, generalized bone tenderness, and a sense of weakness. A waddling gait is often seen. The serum calcium may be normal in osteomalacia, but tends to be low; the phosphorus is almost always low and the alkaline phosphatase elevated. As expected in a condition with deficient calcium, the urinary calcium will be low, except where renal loss of calcium is itself the cause of the osteomalacia.

HYPERPARATHYROIDISM

This condition should present little difficulty in differential diagnosis. As in osteomalacia, almost never will back pain be the only symptom, and although the vertebrae may show only diffuse rarefaction, other bones will reveal the more characteristic lesions of osteitis fibrosa, if the spinal changes are really caused by hyperparathyroidism and not by osteoporosis. Hypercalciuria is usually greater than in osteoporosis, the serum calcium is definitely elevated in all but a very few cases, and the serum phosphorus is almost always low unless there is renal insufficiency. In hyperparathyroidism with bone disease, the alkaline phosphatase is almost always elevated.

PAGET'S DISEASE

Although characteristically leading to enlargement and increased density of bone, Paget's disease may show rarefaction in what Albright has suggested to be the initiating lesion.[9] Although it is possible that osteitis deformans may lead to a radiologic picture similar to that of osteoporosis, to our knowledge this has not been described as involving all of

the lower spine. The characteristic chemical findings of Paget's disease are a normal serum calcium and phosphorus and an elevated alkaline phosphatase. The urine calcium may be normal or increased, depending on whether overgrowth or destruction of bone is more prominent. It is of interest that osteoporosis, with decreased osteoblastic stimulability, and Paget's disease, with localized increases in osteoblastic activity, are both common in elderly individuals and may both be severe in the same individual.

CUSHING'S DISEASE, HYPERTHYROIDISM, AND ACROMEGALY

In discussing the etiologic aspects of osteoporosis, specific endocrine abnormalities leading to this condition have been mentioned, and it is of course important that these be distinguished from senile osteoporosis. By the time that Cushing's disease has produced symptomatic osteoporosis, its other dramatic changes are usually present. The typical florid, hirsute moonface, however, may not be marked, and occasionally the correct diagnosis may be reached only by a high index of suspicion. The serum calcium, phosphorus, and alkaline phosphatase tend to be normal; the urine calcium is often high as in other types of osteoporosis. Mild cases of acromegaly may also be difficult to detect clinically. Diagnosis will often be suggested when radiographs of the spine, in addition to showing osteoporosis, demonstrate an increase in the anterior-posterior diameter of the vertebrae. Also, the serum phosphorus is often elevated, although the serum calcium and alkaline phosphatase are normal. The urine calcium tends to be increased. More prone to be overlooked as a cause of osteoporosis is hyperthyroidism, the symptoms of which are often mild in elderly persons. Such masked hyperthyroidism and low-grade thyrotoxicosis most often lead to osteoporosis, for the condition continues for a longer time than in evident cases. The The serum calcium and phosphorus values are usually normal; the urine calcium is usually increased. Determination of the basal metabolic rate, of thyroidal uptake of radioactive iodine, and of the serum protein-bound iodine may all be necessary for diagnosis, and occasionally, if they are normal or borderline, clinical impression may justify antithyroid medication.

OSTEOARTHRITIS AND HERNIATION OF THE NUCLEUS PULPOSIS

The condition variously known as lumbago, slipped disk, fibromyositis, or sciatica—each of which is possibly caused by herniation of a nucleus pulposus—may also bring the elderly patient to the physician with the complaint of back pain.[10] Since some degree of osteoporosis and of osteoarthritis may be expected in all elderly patients, it is often impossible to tell how much of the symptomatology is due to osteoporosis and how much to one or another of the other conditions.

In all cases in which history and physical examination suggest only the diagnosis of osteoporosis, our practice is to obtain a routine urinalysis and hemogram; radiologic examination of the spine; determinations of serum calcium, phosphorus, alkaline phosphatase, and a protein partition; urine examination for Bence-Jones protein; and quantitative determination of urine calcium.

Treatment of Senile Osteoporosis

Today the symptomatic treatment of osteoporosis usually presents few difficulties. However, some current practises, although effective against symptoms, tend to increase the underlying pathology and encourage complications.

Since the predominant symptom is pain, and the major danger is further fracture, both of which may worsen on motion, various means of immobilization of the spine are often prescribed. Immobilization, by decreasing stresses and

strains, reduces the stimulus to the osteoblasts to produce bone and therefore runs the risk of worsening the condition and preventing further activity. The aim of all treatment should be rapid and complete mobilization. After a fracture, the acute pain often subsides spontaneously within a few days to weeks, but even during this time it is wise to encourage activity if at all possible. When pain is more persistent, efforts at mobilization are even more mandatory. Strong analgesics may be necessary initially, but the analgesic standby is aspirin, which is often quite satisfactory after the initial acute pains have subsided. Rarely, a nerve block may be required to relieve pain and to permit mobilization. To provide support without fixation, we would suggest a corset rather than a brace or, occasionally, a light partial back brace. It is better if these devices are used only for periods of prolonged activity or for a limited number of hours each day. Once mobilization has been effected, a systematic program of physical therapy should be instituted, with mild exercises and some walking each day as a minimum. Caution is necessary and the patient must be warned against strenuous activity which might jar the spine.

Therapeutic radiation has been recommended for relief of pain, but weighed against the small evidence of benefit is the possibility that it may further interfere with processes of bone repair. Therefore, it should probably be avoided.

The variable course of symptoms in the natural history of osteoporosis makes difficult the assessment of symptomatic treatment. It also makes difficult to evaluate by means of symptomatic improvement the forms of treatment aimed at arresting or reversing the underlying pathologic condition. As already noted, severe deformity and multiple fractures may be quite unaccompanied by symptoms. Once symptoms have occurred, they may subside spontaneously, may be intermittent, or may be progressively acute or chronic, with varying degrees of severity. To date, no series of treated or untreated patients has been studied which has been large enough for valid conclusions to be drawn. In reviewing groups of treated patients, one suspects that a similar series of untreated patients might have equivalent prognoses.

Since osteoporosis is usually evident by radiologic examination at the time when symptoms occur, one might hope that change in the roentgenogram would be helpful in assessing definitive therapy. Unfortunately, a number of factors preclude this possibility.

It is estimated that osteoporosis becomes evident radiologically when 10 to 60 per cent of the bone calcium has disappeared. For the skeleton to lose or regain 30 per cent of its calcium at the rate of 100 milligrams per day would require nine years. Although the rate of loss or of theoretic replacement of substance is probably not uniform throughout the skeleton in senile osteoporosis, and although a loss or gain of 100 mg. of calcium per day is only an approximation, the calculation gives a rough idea of the slowness with which the pathology and the radiologic picture might be expected to change.

The difficulty of taking standard films, and of being certain that changes are not just a matter of differing x-ray technic, further complicates the problem. It is to be hoped that improved technics and standardizations for quantitating small differences in bone calcium content may become available.

Some trabeculae seem to disappear completely as osteoporosis advances, raising the question of whether all the lost bone is even theoretically replaceable unless there is a structure on which it can form. Once fracture of a vertebra has occurred, it is also doubtful if recompression of the senile disk and reconstitution of normal bone contour can take place. Occasionally the overgrowth of bone at the site of a fracture may

give the appearance of a return to normal bone structure.

Therefore, it is not surprising that little convincing radiologic evidence has been produced to support claims of improvement by particular therapies. Clarke's films of one patient before and after three years of hormonal therapy are the only ones we have seen which do appear to show definite improvement.[11]

At present, the only means of assessing treatment is by carefully controlled balance studies. Since the body is normally in calcium balance, with 99 per cent of the body calcium in the bones and teeth, and with a constant ratio of calcium to bone matrix, it follows that balance means equivalence of bone resorption and bone repair. Similarly, a negative balance indicates diminishing bone mass, as in osteoporosis, while a positive balance indicates growth or excess of bone repair over bone dissolution. If a patient with known osteoporosis, in negative balance, can be shown to revert to balance, or to enter into positive balance as a result of a specific form of treatment, then it can be inferred that the underlying process has been halted or reversed.

The only form of treatment thus far shown to reverse the negative balance found in senile osteoporosis is therapy with sex hormones. This lends support to the theory that at least a partial cause of this condition is the excess of antianabolic over anabolic hormones which occurs with advancing age.

TREATMENT WITH SEX HORMONES

Several investigators have shown that a negative balance can be reversed and positive balances induced and maintained in postmenopausal women treated with estrogens.[12-16] It has also been shown that, once a maximum effect has been attained in the woman treated with estrogen, androgens will produce a further increase in the positive balance.[12,13] The male hormone has the further advantage of strengthening muscle, thereby giving greater support to bone. Fewer studies have been performed in men patients, and such studies would be desirable. On present evidence it appears that testosterone is most efficacious in the male, and that estrogens have an additive effect. It has been the impression of these investigators that such hormonal therapy hastens the amelioration of symptoms and, if continued, may lessen the incidence of further difficulties.

It has been our practice, once a diagnosis of osteoporosis has been made, to initiate treatment in female patients with both an estrogen and an androgen. Diethylstilbestrol (stilbestrol), which is inexpensive and can be administered by mouth, is the estrogen most commonly employed, in doses varying from 1 to 5 mg. daily for four or five weeks, then omitted from seven to ten days. If stilbestrol produces nausea which is not reduced by taking the medication at bedtime, conjugated estrogenic substances, in the form of Premarin, in doses of 1.25 or 2.50 mg. per day, or Ethinyl Estradiol, in doses of 0.1 to 0.2 mg. per day, may be prescribed in a similar regimen. If oral medication is not tolerated or is otherwise contraindicated, 5 mg. of estradiol dipropionate may be injected once weekly for four weeks and then omitted for one week. Higher doses seem to have little further effect, which is consistent with the failure to change calcium balance by estrin administration to premenopausal women. The four- or five-week administration usually permits sufficient building up of the endometrium so that bleeding occurs when estrin is withdrawn. Giving sufficient amounts cyclically will prevent metropathia and menorrhagia, and the regularly induced bleeding is itself some assurance that the genitalia remain normal. The patient is requested to keep a chart of medications and of periods, and any irregular bleeding should be promptly investigated. Be-

cause of the theoretic possibility of estrin carcinogenesis – for which, however, there is almost no clinical support–pelvic examinations and vaginal smears are made routinely twice a year.

Occasional patients experience hot flashes each time estrin is withdrawn. In such cases, estrin may be given continuously, menstruation being obtained following five-day courses of progestational hormone, pregneninolone, every five weeks. This is given orally in 10-mg. tablets, five times daily for five days. If injections are preferred, 5-mg. doses of progesterone may be given each day for five days. In the rare patient who fails to respond, or who responds with metropathia or menorrhagia to cyclical administration of estrogen, a similar program of estrogen and progesterone may regulate bleeding. In some elderly women, estrogen and progesterone in any dose and in any regimen will fail to induce vaginal bleeding, probably because the endometrium has become too atrophic to be stimulated. This is not usually the case, however, even in very elderly patients. In the patient who has had complete total hysterectomy, estrogen alone may be given continuously. Once begun, estrogen is usually continued indefinitely, even though symptoms may have subsided.

Methyl testosterone, in linguets, is the male hormone most frequently administered to our patients. In women, treatment is usually started with 5 or 10 mg. daily or every two days and continued four to eight weeks or until signs of masculinization become troublesome. Some women may tolerate the smaller doses indefinitely, in which case it is desirable to continue administration of both hormones. The combination of estrogen and androgen appears to slow the rate and degree of masculinization which testosterone alone would induce. In the doses used, testosterone does not often inhibit estrogen-progesterone or estrogen-withdrawal bleeding, but it may contribute to the failure of these hormones to induce menstruation.

In men, treatment is usually begun with both estrogen and androgen. The androgen is continued indefinitely, and the estrogen until side effects become disturbing. Two or three 10-mg. linguets of methyl testosterone may be given daily, or, if injections are preferred, 50 mg. of testosterone propionate three times weekly. The long-acting testosterone esters – testosterone cyclopentylpropionate, testosterone enanthate, and so on–may be given in doses of 100 to 250 mg. every two to four weeks. Estrogen, most often stilbestrol in doses of 1 to 2 mg. daily, is usually well tolerated for one to two months before mastodynia, gynecomastia, or decreased libido occurs. As with testosterone in women, combined therapy may be tolerated for prolonged periods or indefinitely without untoward effect. In the hormone-treated male, prostatic examinations should be made regularly, and determinations of the acid phosphatase from time to time may be reassuring. Here again, there is no clear-cut evidence of carcinogenicity, but it is well-known that testosterone may accelerate the growth of an existing prostatic carcinoma.

Aside from those already mentioned, there are almost no contraindications to hormone administration to older patients. Although estrogens may induce fluid retention, it is rarely significant with the doses given. When fluid retention is already present, it should be treated before hormones are prescribed. The fluid retention induced by testosterone is slight and is probably never a clinical problem. Libido in the female is rarely modified by estrogens, but may be enhanced by androgens, sometimes uncomfortably. This is usually minimized by combined therapy. In the male, the diminution of libido by estrogens may also be overcome by combined therapy. In the rare older male who is concerned

with fertility, it should be remembered that both estrogens and testosterone may inhibit spermatogenesis and that the inhibition may be permanent after withdrawal of these hormones. The severity of the osteoporosis usually outweighs such considerations, as it often outweighs the concern over virilization or feminization.

CALCIUM, PROTEIN, AND VITAMIN REQUIREMENTS

Although osteoporosis is not primarily a disorder of calcium metabolism, many physicians continue to prescribe calcium and vitamin D in treating it, often in alarmingly high doses. Since neither of these stimulates matrix formation into which calcium may be deposited, the only result is a further increase in the already elevated urine calcium with an added risk of renal stone formation. We would suggest that vitamin D never be given in the treatment of uncomplicated osteoporosis.

The need for additional calcium will depend on the patient's usual intake, which can be readily calculated. The requirement of normal adults is still debated, although it is generally placed between the 560 mg. per 70 kilograms per day suggested by Outhouse[17] and the 840 mg. per 70 kilograms per day as suggested by Steggarda.[18] There is less agreement from studies on older patients. Bogdonoff concludes that 850 mg. per day is the approximate requirement;[19] Roberts calculates a requirement of 987 mg. from studies on 9 elderly women;[20] and Ackerman's approximation is 1,295 mg. from a study of 7 elderly men.[21] Several investigators report the need for higher intakes of calcium during estrogenic treatment of osteoporosis.[13,22] We would favor a diet containing approximately 1,000 mg. of calcium per day, although we believe this to be somewhat above the required amount.

In going from negative balance to equilibrium, cessation of hypercalciuria would obviate the necessity of an intake above normal. Since the positive balance obtainable with hormones is rarely greater than 200 mg. per day, an intake of 1,000 mg. of calcium per day would not be a limiting factor to bone repair. One thousand milligrams is somewhat more than the content of a normal diet which does not include milk by the glassful—such a diet usually containing from 500 to 800 mg. of calcium. One glassful of milk contains 275 mg. of calcium, and this, plus a normal diet, should be sufficient. When milk is not tolerated, or when the calcium content of a diet acceptable to the patient is too low, calcium lactate tablets may be given. Five grams of this material contain 650 mg. of calcium.

As senile osteoporosis is not caused by protein deficiency but by an inability to utilize protein, it should be determined whether the diet contains adequate protein. Beyond this amount protein supplements are unavailing. We usually prescribe a diet containing from 1 to 2 gm. of protein per kilogram of body weight, or higher if the diet has actually been deficient.

Similarly, vitamin supplements are probably unnecessary if the patient has been receiving a well-balanced diet. It is reported that, in elderly persons, the blood levels of ascorbic acid tend to be lower than those of adults.[23] Because of this and because osteoporosis may occur with scurvy, we have frequently given supplementary vitamin C, but without much conviction that it is efficacious.

STRONTIUM

Strontium has been recommended in the treatment of senile osteoporosis,[22] but there is little evidence that it behaves differently from calcium. There is the possibility that, being heavier than calcium, mol for mol it may give greater strength to bone, but this remains unproved.

PROPHYLACTIC TREATMENT

Sex hormone administration would appear to be advisable not only in patients with symptomatic senile osteoporosis, but in certain other groups of elderly patients as well. In the older person who is immobilized for any cause, such treatment may partially prevent the threat of enhanced osteoporosis. The high incidence of fractures of the wrist, hips, and other bones which follow mild trauma in elderly persons undoubtedly reflects osteoporosis, which will be worsened by bed rest or other forms of immobilization required in treatment of the fractures. This group should therefore also be considered as candidates for hormonal therapy. The hazard of severe osteoporosis in patients treated with cortisone has been emphasized.[24-26] The danger may be lessened by the judicious use of sex hormones,[26] although cortisone should be avoided in elderly patients if at all possible.

A vibrating bed has been shown to reduce calcium loss in normal persons who are kept in bed.[27] By analogy, it may be helpful in providing stresses and strains to the bones of immobilized osteoporotic patients.

From the Department of Medicine of the Harvard Medical School and the Massachusetts General Hospital, Boston.

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Benign lesions of the lower esophagus in the aged

F. JOHNSON PUTNEY, M.D.
PHILADELPHIA, PENNSYLVANIA

Symptoms referable to the esophagus cannot be discounted until thorough examination of the patient has been carried out. Both roentgen study and esophagoscopic examination are necessary in most instances for accurate diagnosis. In the aged, treatment may be directed toward relief of symptoms by conservative measures. Surgical excision and histologic study may be necessary for final diagnosis.

◆ Benign lesions of the lower esophagus are difficult to diagnose accurately for they may be confused with diseases of other organs or malignancy in the esophagus itself. They present numerous and varied symptoms, and the diagnosis depends upon thorough roentgen and esophagoscopic study. In the majority of elderly patients, treatment can be directed toward relief of symptoms rather than toward complete eradication of the lesion. Surgical interference with the normal esophagogastric pinchcock mechanism should be avoided in all cases. Disruption of this mechanism results in reflux esophagitis with regurgitation and pain so that the original symptoms become more pronounced or additional symptoms are added to those present. The principal benign lower esophageal lesions are hiatal hernia, achalasia, diverticulum, varicosity, and tumor.

Esophageal Hiatal Hernia

Esophageal hiatal hernia may simulate other lesions of the gastrointestinal tract, cardiac disorders, or pulmonary diseases. At times a small hiatal hernia found on roentgen examination is passed over as being of no significance when, in reality, it is the source of the difficulty. The amount of mechanical interference with the herniated stomach, the degree of diaphragmatic dysfunction, and the amount of increased intrathoracic pressure determine type and number of complaints regardless of size of the hernia.

Clerf and associates found that the two outstanding symptoms were dysphagia and pain,[1] so that, when these two symptoms occur together, the possibility of a hiatal hernia should be considered. In some patients, the swallowing difficulty is referred to the cervical region so that attention may be focused entirely on the cervical esophagus and the lower esophagus disregarded.

The chief difficulty in diagnosis comes when there are one or more concomitant conditions and it becomes necessary to determine which lesion is actually producing the symptoms. Many older individuals have clinical and electrocardiographic evidence of myocardial insufficiency or coronary artery disease and the pain may be attributed to these causes. Electrocardiographic findings alone cannot be relied upon when the pain and associated symptoms suggest a hiatal hernia. In many cases, the pain

F. JOHNSON PUTNEY *is associate professor of laryngology and bronchoesophagology at Jefferson Medical College, Philadelphia.*

simulates that caused by a cardiac disorder, for it is located either precordially or radiates upward into the shoulder or down into the abdomen, is not constant, and occurs in attacks which vary from a few minutes to hours. When there is severe radiating pain with other evidence of myocardial or coronary insufficiency, it is easy to explain all of the symptoms on this basis. Some patients are treated for years for cardiac disorders with no relief, yet, when treatment is directed toward the hernia, relief follows. In hiatal hernia, the pain comes on during rest, and frequently occurs at night when the gastric acidity is high, allowing reflux esophageal inflammation.

Cholecystitis with or without gallstones frequently occurs in conjunction with esophageal hiatal hernia, and many patients have their gallbladders removed without relief of symptoms (figure 1).

Peptic ulcer is sometimes associated with hiatal hernia, for hyperacidity plays a part in development of both conditions, and, although it is not responsible for the actual hernia, it causes esophagitis. The pain of peptic ulcer and hiatal hernia are alike, but frequently some degree of dysphagia and sticking or lodgement of food is found in the latter. Since the medical treatment of both lesions is similar, when they coexist and improvement follows treatment, it may not be possible to determine which lesion was actually responsible for the symptoms.

Two patients have been observed with respiratory complaints and with paralysis of the right side of the larynx, presumably due to interference with the right recurrent laryngeal nerve. No other cause could be found and, although there are many cases of laryngeal paralysis in which the cause remains obscure, occurrence of hiatal hernia and paralysis suggests an etiologic relationship.

The lower esophagus and cardiac end of the stomach are so difficult to examine, both roentgenologically and esophagoscopically, that one cannot depend entirely upon either method for diagnosis. Esophagoscopic study should be made of patients with symptoms but with negative roentgen studies, for this may establish the diagnosis. In addition, the patients in whom hiatal hernia has been demonstrated by x-ray examination should be examined esophagoscopically to determine the presence or absence of esophagitis. There also may be superficial ulceration which can be detected endoscopically and, if bleeding has occurred, it is imperative to search the esophagus for the bleeding site.

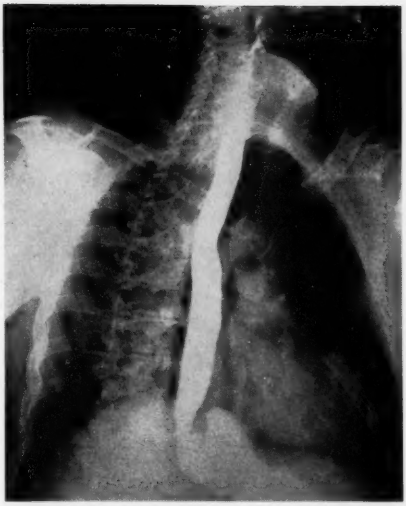

FIG. 1. *Moderately large esophageal hiatal hernia with symptoms simulating cholecystitis. Symptoms continued after cholecystitis, indicating that they were caused by the hiatal hernia.*

Even though there is no hernia, incompetency of the hiatal pinchcock occurs in many cases, resulting in regurgitant esophagitis with nocturnal pain and other symptoms of hiatal hernia. Incompetency of the hiatus, which is rarely demonstrated roentgenologically but can generally be seen esophagoscopically, is associated with regurgitation of gastric juice and degrees of esophagitis. Cardioesophageal relaxation probably repre-

FIG. 11. *Dilated esophagus with smooth constriction at hiatal level suggestive of achalasia, but caused by adenocarcinoma of fundus of stomach with submucosal extension to lower esophagus.*

sents the first step in the formation of hiatal hernia. Later, the stomach occupies a supradiaphragmatic position.

Surgical repair is rarely indicated in the aged unless there is actual or threatened strangulation or serious hemorrhage which cannot be controlled by other means. In the majority of elderly patients, symptomatic treatment gives relief. Conservative treatment is directed toward providing an adequate passageway for food and the relief of pain. In the occasional case in which mechanical treatment is necessary to enlarge the lumen, it can be done by dilatation over a previously swallowed thread. The frequency of dilatation depends upon the type and severity of the constriction. For ulceration which does not respond to dietary and medical treatment, topical applications of a mild silver solution are beneficial. If pronounced esophagitis is observed, a modified peptic ulcer regimen with strict regulation of the diet may be employed. Liquids should be taken with meals to aid in washing down food, and postural measures should be employed to encourage food passage so that it does not lodge in the hiatal sac. Reclining after meals should be discouraged for it occasionally may produce epigastric fullness. In many cases pain can be relieved with antispasmodic and antacid drugs, together with frequent feedings. Nocturnal pain is relieved if the patient is propped up on several pillows during sleep. Elderly patients who are not relieved by these measures can be helped by the relatively simple procedure of phrenic exeresis. When surgical repair is being considered for the aged patient, it is wise to first perform a phrenic exeresis, for the symptoms may improve to the point where further operative treatment is not needed.

Achalasia

Achalasia, or cardiospasm, commonly begins early in life and, by the time the patient has reached middle age, has usually been present for some time. In a review of 286 cases at Jefferson Hospital, there were only 32 patients in the 60 to 70 age group and 4 patients over 70.

When the disease has a sudden onset, the initiating factor may be psychogenic. Although this is less apt to occur in older people, who are subject to less stress and strain than younger persons, there may be occasions in which mental disturbances give rise to achalasia. Pre-existing achalasia, which has been quiescent, may be activated in the elderly with a sudden unfavorable change in the environment.

Before the diagnosis of cardiospasm is made in the elderly patient, carcinoma must be eliminated. Since carcinoma and achalasia may have a similar appearance on the roentgen film, routine esophagoscopy should be performed to rule out possible malignancy. This is especially necessary in cases of carcinoma of the

fundus of the stomach in which the malignancy extends submucosally into the lower esophageal segment producing narrowing without ulceration, simulating the smooth constriction found in cardiospasm (figure II). Since patients with achalasia often lose much weight, when food fails to reach the intestinal tract, carcinoma may be suspected on this basis alone.

In uncomplicated achalasia, esophagoscopic examination reveals no constriction at the hiatal level and the esophagoscope can be easily introduced into the stomach. This is contrary to what might be expected on the basis of the apparent constriction shown on the roentgen film. On esophagoscopic examination, actual stenosis at the esophagogastric junction suggests submucosal carcinoma with infiltration. When carcinoma has ulcerated through the mucosa, the tissue can be examined histologically, but more often the mucosa remains intact and the diagnosis of malignant change has to be based on rigidity and stenosis.

Outstanding symptoms are dysphagia and regurgitation, followed by weight loss and pain. Respiratory symptoms are caused by aspiration of esophageal contents or pressure from the distal esophagus, producing wheezing, dyspnea, hiccup, and occasional hoarseness. The dysphagia is usually identical for fluids and solids, with considerable discomfort from cold liquids. Ice cream may cause difficulty and raw apple is another chief offender. Obstruction is so complete that food may remain in the esophagus for days and may be regurgitated as the organ fills up. The obstruction is usually localized at the epigastrium but, when the entire esophagus is occupied by food, cervical discomfort is experienced.

Regurgitation is commonly delayed for periods of several hours to days after eating. Fermentation occurs in varying degrees so that, on regurgitation, the material presents a characteristic appearance. The absence of gastric juice and digested food in the regurgitated material suggests achalasia rather than obstruction in the lower gastrointestinal tract. When small amounts of food pass through into the stomach, regurgitation is less noticeable, for the esophagus becomes slowly decompressed without the overdistention of complete blockage. Esophagitis and superficial ulceration develop when food remains in the esophagus for a long period, and it is not uncommon for small amounts of blood to be regurgitated with food. Frank hemorrhage is not a serious factor and generally requires no active treatment.

There is little indication for surgical treatment in the elderly patient, unless the symptoms cannot be relieved otherwise. Mechanical dilatation of the hiatus has given satisfactory results in the majority of cases. After the patient has swallowed a thread, dilatation and actual avulsion of the muscle fibers at the hiatus are performed, using the thread as a guide. There is some danger of peritonitis or mediastinitis with this procedure, but little relief occurs unless the musculature is actually avulsed. Passage of uniform sized bougies does little to eliminate the obstructive symptoms. It is not often necessary to dilate patients after the first several treatments, and dilatations may be spaced as far apart as six to twelve months.

In many cases of long standing, the lower esophagus is not only dilated but assumes a tortuous and almost sigmoidal curvature. In these patients, it is almost impossible to dilate the hiatus mechanically, so that something further may be needed in the way of treatment. The Heller esophagocardiomyotomy has given the best results in the uncomplicated cases requiring surgical treatment, but in the type with sigmoidal dilatation this procedure is insufficient. Any attempt at radical surgical removal by excision of a portion of the lower esophagus gives temporary improvement but may later result in obstruction and stenosis.

FIG. III. *Epiphrenic esophageal diverticulum with large mouth and mild obstructive symptoms.*

Epiphrenic Esophageal Diverticulum

This infrequent pulsion type of diverticulum is located within a few inches of the hiatus and is essentially a herniation of the mucous membrane through the muscle coats produced by pressure from within. The symptoms are similar to those of other lower esophageal lesions and usually progress with an increase in size of the sac. When the sac becomes large enough to retain food, thus producing distortion and compression of the subdiverticular esophagus, obstructive symptoms appear. The mouths of the diverticula are large and only after the sacs become filled will food overflow into the esophagus and enter the lower gastrointestinal tract.

The x-ray picture may be confused with that of achalasia in which there is a sigmoidal dilatation of the distal esophagus, or with that of carcinoma when it produces a false diverticulum above a stenosis. In the uncomplicated epiphrenic diverticulum, there is a smooth, uniform, sacular dilatation involving the entire circumference (figure III).

In patients with asymptomatic diverticulum, no treatment is required. Usually these patients get enough nourishment so that there is no great weight loss and the diverticulum rarely produces enough subdiverticular obstruction to prevent sufficient food from entering the stomach. Patients have been observed who have maintained nutrition and carried on their daily activities for twenty years on medical therapy. Rigid control of the diet is necessary, for obstruction develops as soon as the diverticular pouch becomes overloaded or the patient eats coarse food not thoroughly chewed. The patients frequently empty the diverticulum themselves by taking large quantities of fluids, lying flat, and lowering the head. The lesion can be removed by operation, but this should be reserved for the younger patient.

Esophageal Varicosities

Varicose veins are common in the lower third of the esophagus secondary to portal hypertension. Patients usually have cirrhosis of the liver with an intrahepatic block resulting in portal hypertension and leading to enlargement of esophageal veins. In a smaller group, varicosities are secondary to extrahepatic lesions, such as obliteration of some of the portal vein radicals and thrombophlebitis of the portal system.

The chief complaint and principal danger from varicosities is hemorrhage. Although bleeding from esophageal varices accounts for only a small number of cases of massive upper gastrointestinal hemorrhage, it is responsible for more than 50 per cent of the fatalities in this group. As the cirrhosis progresses and the patient ages, he is more prone to symptomatic esophageal varicosities.

It has recently been shown that esophageal varicosities are variable and, although they may be detected at one examination, may not be present at the next.[3] The diagnosis is more apt to be made after a patient has experienced a bleeding episode, for then the varicosities are dilated and fragile.

The diagnosis can be made by roentgen study in a certain group of cases provided the varicosities are large (figure IV). Esophagoscopic examination is the most satisfactory method of diagnosis. If examination is done soon after bleeding, the percentage of positive diagnoses can be raised to double that obtained by roentgenologic study. Examination should be repeated at various intervals if symptoms point to esophageal varicosities and they are not found at first examination. Friedberg reports a positive diagnosis by esophagoscopy in 50 per cent of patients as compared to 30 per cent found by roentgen study.[2]

Only positive findings are significant in diagnosis; negative findings do not exclude varices. At esophagoscopy, submucosal dilatation of veins with their bluish color is not easily confused with other esophageal lesions. Esophagitis occurs occasionally in conjunction with varicosities, and it then becomes a problem to know whether varicosities are present for the esophagitis obscures their typical appearance. Associated hiatal hernia is not infrequent and, when the folds of the lower esophagus are large, a definite diagnosis may not be possible.

When a patient is admitted to the hospital with severe gastrointestinal bleeding, esophagoscopy immediately helps to establish the source of the bleeding and can be done without shock or harm to the patient. Esophagoscopy is especially useful if peptic ulcer is suspected and it cannot be determined whether this or varicosities are the source of the bleeding. If the bleeding is located in the lower esophagus, the Sengstaken tube is probably best suited

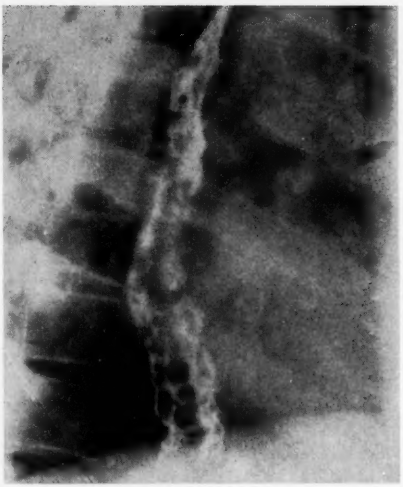

FIG. IV. *Esophagogram of large lower esophageal varices.*

to control the hemorrhage. Inflation of the tube exerts pressure both on the lower esophagus and upper end of the stomach with compression of the esophageal and gastric veins. The tube can be kept in position while the patient is supported and blood volume replaced.

When bleeding persists, sclerosing injection of the esophageal varicosities may be beneficial. Only a few veins can be sclerosed at a time, so that it is necessary to inject one or two veins at a sitting and repeat this at intervals. Only the visible veins in the esophagus can be so treated; many veins in the esophagus and stomach are not injectable. Disconcerting is the fact that, after apparent sclerosis of esophageal varicosities, no thrombosis can be demonstrated at autopsy. Injection therapy has definite limitations and probably should be reserved for splenectomized patients with severe esophageal hemorrhage.

Benign Tumors

Benign tumors of the esophagus are rare and generally occur in the older age

FIG. V. *Filling defect in lower esophagus caused by smooth muscle tumor.*

group. Leiomyoma and polyp are the most common and are often symptomless. Although such tumors may arise in any portion of the esophagus, they often develop in the lower third and are manifested by obstructive symptoms with dysphagia.

Roentgenograms may demonstrate an obstruction from an intraluminal mass, a tumor in the muscle wall, or an extraesophageal lesion producing compression stenosis, as shown in figure V. The diagnosis may not be evident on roentgen examination, for small tumors of the polypoid type may not be seen, while larger tumors may be confused with achalasia because of obstruction and dilation of the esophagus above the lesion.

The diagnosis may be missed on esophagoscopic examination because extraluminal tumors do not alter the mucous membrane and, as the esophagoscope is passed beyond the lesion, the polyp or soft tissue mass becomes compressed laterally. Even when a tumor is seen, it is often not safe to remove tissue for histologic examination for the necessary cutting through intact mucous membrane may lead to ulceration and subsequent infection. In leiomyoma, constriction with an intact mucosa lacking the firm stenosis associated with carcinoma is observed. Although esophagoscopic examination aids in establishing diagnosis, a normal examination does not exclude presence of a benign tumor.

Histologic demonstration of benign tissue may be misleading for, if malignancy is present, it is usually at the base of the tumor. I recently observed two patients, each with a polypoid lesion visible both on roentgenography and esophagoscopy, who had a histologic report of benign tissue. When the patients were operated upon and the apparently benign lesions excised, areas of ulceration were found at the base of the tumors. Study of frozen section proved these to be carcinoma, making it necessary to proceed with radical resection.

In the aged patient, symptoms produced by benign tumors of the lower esophagus are rarely severe enough to warrant surgical removal, but such removal is frequently necessary to establish a definite diagnosis. The disability and mortality is not high provided simple excision can be performed. When the lesion has been present for many years with no increase in size and few symptoms, one may feel justified in assuming that it is a benign lesion, but, in the lower esophagus, malignancies far outnumber benign tumors. Surgical excision is the safest procedure and should be carried out unless the benign nature of the tumors has been positively established by other means.

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Allergy in the geriatric patient

SOLOMON SLEPIAN, M.D., and
JACOB REICHER, M.D.
BROOKLYN, NEW YORK

Allergies may first occur in old age or may be carried over from youth. The seeming benignity, the danger of asthma after 40, difficulties of skin test interpretation, and necessary modification of allergic management are a few of the features of allergy peculiar to the geriatric patient.

◆ Although allergic disease seems to be predominantly a disturbance of the young and middle-aged, this does not mean that allergy may not manifest itself for the first time in an old person, nor that the various allergies may not continue to be active in the later years of life. However, the incidence of certain of the allergic manifestations in the aged differs from that in young people. There are also certain features of allergy in the aged which require the special interest of the physician trained in geriatric medicine. Such features are: (1) the seeming benignity of allergy in old people on the one hand and (2) the greater hazard to life of asthma starting after 40 on the other; (3) the difficulties in the interpretation of skin tests in the aged; and (4) the occasional onset of severe seasonal hay fever in an aged person despite the belief that hay fever does not start late in life.

Attenuation of Symptoms

It seems to be generally true that in individuals who have had allergies from early life, symptoms lessen in severity with age or, at times, disappear entirely. This may occur without specific treatment or general allergic management. Loss of symptoms may come about because specific sensitivities tend to have limited duration and "wear out," so to speak, although it sometimes takes many years for this to happen. However, while sensitivity to some substances disappears, hypersensitiveness to others may become manifest. There is also the possibility that sensitivity may take a new form—that is, produce a new type of clinical reaction. A patient may cease having nasal allergy from a specific food but may find the same food now produces urticaria or gastrointestinal symptoms.

The reason for this apparent attenuation of the allergic state is not clear. It may come because of certain physiochemical changes in the cells incident to the aging process. A characteristic of the allergic response is its explosiveness, or vigorous action. Because of endogenous changes, the cells in the shock tissue of most aging persons lose the ability or do not have the vitality to support a vigorous immunochemical reaction. Yet the immunology of the allergic state—the fundamental physiochemical reactions which result in the clinical manifestations of allergy—is said to be the same in the geriatric patient as in the young, only the threshold may be altered.

SOLOMON SLEPIAN *is attending allergist, Jewish Chronic Disease Hospital and Brooklyn Eye and Ear Hospital, Brooklyn.* JACOB REICHER *is attending allergist, Jewish Chronic Disease Hospital and Long Island College Hospital.*

Reliability of Skin Tests

When skin tests are employed to detect offending allergens, the geriatric patient presents special problems. Even in young patients, some allergists rely very little on a positive skin test for determining the etiology of a given case, except in testing for pollen sensitivity. In aged patients, the reliability of the skin test is even more questionable. The dry, atrophic skin of the senescent person reacts poorly to allergens. The scratch test particularly gives feeble reactions, and incidence of positive reactions to foods becomes less in older people. After 50, only a few give positive reactions, although, in many instances, clinical signs and symptoms and therapeutic results seem to indicate hypersensitivities to food stuffs.

Nevertheless, we must be aware of the occasional aged patient who responds very actively and severely to skin tests. Wiseman and McCarthy-Brough report the death of a 78-year-old woman following intradermal testing,[1] and emphasize that the aged person requires the same meticulous care in testing and treatment as patients of any other age group. In spite of their fallibility, skin tests should be made in any case in which the offending substances cannot be detected by any other methods.

Latent Allergy

In the majority of instances in which it is claimed that allergy has started late in life, minor allergic symptoms may have been present but unrecognized in early life. Only involvement of a new shock tissue with development of new symptoms may have made the patient suddenly aware of an unrecognized allergic condition. For example, asthma may appear late in life in a patient who has had mild nasal symptoms for years. Unless a very careful history is taken, it will not be apparent that the asthma is simply the involvement of a new shock tissue in a hypersensitive individual and not the first manifestation of allergy.

The following case history illustrates the tardy appearance of latent allergy:

The patient, M. G., was 59 when asthma first appeared. About two years before, he had fractured his left femur. While he was immobilized with his leg in traction, a thrombosis developed in the right leg, followed by embolization to the lung. While he was convalescing in Florida, he began to have tightness in his chest, wheezing, and shortness of breath. Within a few months he had almost daily attacks of dyspnea, cough, and expectoration of froth and occasionally of thick yellowish mucus. His attacks were worse on slight exertion or during change in weather. He had had mild nasal discomfort for many years and at 54 had nasal polyps removed. There were no other manifestations of allergy and no allergy in his family.

He was admitted to the hospital in asthmatic crisis. His temperature was normal during the entire two weeks of hospital residence. Pulse ranged near 100. Blood pressure was 130/80. Leukocyte count was 13,700 and blood eosinophilia was 11 per cent. Laboratory findings of urine, sedimentation rate, Wassermann, blood sugar, blood urea nitrogen, serum total protein, albumin, globulin ratio, and cholesterol were all normal. Chest roentgenogram revealed slight hyperillumination of the superior lung fields, no evidence of fibrosis, and no depression of diaphragms; the heart shadow was not enlarged. The reading was that of early emphysema. An electrocardiogram showed small QRS complexes in the limb leads. The interpretation was that of mild nonspecific abnormalities consistent with pulmonary emphysema.

Studies were made of pulmonary function, vital capacity, maximum breathing capacity, and oxygen saturation in arterial blood. The conclusions were that the patient had marked impairment of the ventilatory capacity caused by asthma of undetermined origin, with no evidence of heart disease or left heart decompensation complicating the bronchial asthma.

Scratch and intradermal skin tests showed the patient to be sensitive to kapok, rabbit hair, mixed feathers, house dust, tobacco, and a number of foods. There were no positive reactions to pollens.

He improved on a modified cereal-free diet, injections of autogenous vaccine, and house-dust extract. He still requires bronchodilators, sedatives, and expectorants to keep him com-

fortable. When there is an exacerbation of symptoms, steroids are administered.

Severity of Asthma

Asthma, either atopic (immediate wheal reacting and strong familial tendency) or nonatopic, is the most important of the allergic diseases in old people. Its prognosis appears to become more serious with the age at onset. In young and early adult life, asthma is controlled rather easily, and is benign as far as danger to life is concerned, despite its alarming morbidity. Bullen studied 176 deaths in which asthma was a primary or contributing cause or in which there was a definite past history of asthma.[2] He found that, in these cases, onset of asthma had come in the fourth, fifth, and sixth decades in contrast to the general age of onset, which is in the first decade. In more than half of the patients studied, death occurred within ten years after onset of symptoms. The vast majority of the cases were of the nonatopic type, in contrast to the atopic form which starts in childhood. The rapid drop in the length of life of patients whose asthma started after 40 suggests that this type of asthma presents a much greater hazard than that which begins in youth.

This seems to be directly related to the fact that the hazard is greater in patients with uncontrolled asthma, for frequent attacks produce scarring, extensive fibrosis, and emphysema. The progressive involvement of the vascular tree from these morbid changes leads to hypertension of the lesser circulation and frequently to sclerosis of the pulmonary vessels. This may eventuate in right-sided cardiac failure. The greater susceptibility of this group to serious respiratory tract infections is an added hazard reflected in the mortality figures.

In older patients, also, a number of clinical conditions may occur which are likely to produce respiratory distress and wheezing and which may be mistaken for allergic asthma. These are chronic bronchitis and emphysema; bronchiectasis; cardiac asthma from left ventricular failure; pulmonary sclerosis; and tracheal and bronchial obstruction or impingement from mediastinal tumors, substernal thyroid, diverticulum of the esophagus, and bronchogenic tumor. Any of these conditions may be found in young people, but they are encountered more often in the geriatric group. They may occur as a single entity and simulate asthma, or the patient may have asthma complicated by one of these conditions. In such an event, diagnosis and management becomes much more difficult.

Seasonal Hay Fever

It is commonly believed that seasonal hay fever or pollenosis does not develop in old people. It is true that, in the vast majority of old persons, seasonal hay fever is carried over from early life. In a study of 222 adult seasonal hay fever sufferers, only about 1.8 per cent had symptoms for the first time after age 50.[3] Hansel found that, in a group of 220 patients aged 15 years and over, with nasal manifestations of allergy, the first symptoms began between ages 51 to 65 in not more than 8.6 per cent.[4] Not only may seasonal hay fever start late in life, but pollen asthma and the other manifestations of pollen sensitivity may also occur.

The following brief histories illustrate patients who developed pollenosis late in life:

J. B., a white male patient, had his first attack of asthma in the spring of 1947 at the age of 59. Wheezing and cough became almost continuous.

In August of the same year, hay fever appeared, with exacerbation of asthma, as well as an attack of urticaria, lasting several days. There was no history of allergy or other disease. He had a positive family history, as his grandfather had had asthma. Skin tests showed him to be sensitive to poplar, ragweed, dust, cat ephithelium, feathers, kapok, tomato, squash, fish, and chocolate.

Positive foods and contacts were eliminated. Iodides, aminophylline, and antihistamines were given as necessary. Hyposensitization with ragweed and dust was carried out during the early summer of 1948. In August 1948, he went to the White Mountains of New Hampshire, and found that his hay fever symptoms were less, but his asthma was worse. He spent three years in Arizona, but his asthma became intractable.

Administration of cortisone resulted in relief of the asthma. He has been on this drug for the last three and one-half years. Except for slight wheezing, he is fairly comfortable.

Patient R. S., a white woman, first had seasonal hay fever at age 64, when she was in the hospital for diabetes and amputation of right leg because of gangrene. She also had hypertension and arteriosclerosis obliterans. She had no other manifestations of allergy and no past history of allergy. Her family history was positive; four children had hay fever.

The nasal smear on four occasions showed many eosinophils and there was blood eosinophilia up to 5 per cent.

Treatment

Treatment of allergies in the geriatric patient requires some modification in accordance with the principles applicable to the treatment of the aged. However, unlike the allergies of infancy and childhood, in which a special pediatric allergist is often called upon for treatment, the skill of the general allergist is adequate for management of the geriatric group without evoking a new group of specialists.

From the Allergy Service, Department of Medicine, Jewish Chronic Disease Hospital, Brooklyn, New York.

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THE PSYCHOTHERAPIST dealing with aged persons can act as a substitute parent at the beginning of therapy. The course of treatment should be conducted so that the patient feels the therapist has been won over as an ally. After this relationship is established, a more realistic pattern can evolve. Although aged patients appear depressed and helpless, the feelings of frustration and failure may be externalized so as to obtain care from and power over other people and the environment.

A. I. GOLDFARB: Psychotherapy of aged persons. IV. One aspect of the psychodynamics of the therapeutic situation with aged patients. Psycho. Rev. 42: 180-187, 1955.

IN AN ANALYSIS of basic nutrition data on 577 healthy volunteers over 50 years of age, it was found that nutrition influences health and longevity. In contrast to common belief, the higher the serum cholesterol level in persons over 70, the lower the mortality rate. Death rates in individuals with a low blood level of vitamin A, niacin, and ascorbic acid are higher than in subjects with normal or high levels. Preservation of teeth bears a direct correlation to blood ascorbic acid content.

Mortality is four times higher in subjects with a systolic pressure over 180 mm. of mercury than in those with systolic pressure under 140. Diastolic pressure shows little correlation with mortality rate. Mortality from cardiovascular-renal disease in overweight individuals is nearly double that of individuals of average weight.

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The aged shoulder

S. M. ALBERT, M.D., D. M. SKLAROFF, M.D.,
A. M. RECHTMAN, M.D., and H. SCHRAER, Ph.D.
PHILADELPHIA, PENNSYLVANIA

A statistical analysis of 250 aged shoulders showed that calcific deposition is greater with advancing age, is more frequent among women, has no clinical significance, and does not adversely affect joint motion.

◆ The "aged" shoulder may be an inaccuracy. Perhaps a more complete title would be "the aged shoulder in the aged," for present knowledge and clinical experience indicate that a shoulder may grow old at almost any age after puberty and remain young in old age.

This study was carried out on a group of 125 residents of the Home for the Jewish Aged in Philadelphia, most of whom had asymptomatic shoulders. The group consisted of 80 women and 45 men, with an average age of 80.1 years.

Calcification

Of the 250 shoulders reviewed, 55 showed varying amounts of calcific deposit in the rotator cuff and 195 were completely negative. Of those 55 shoulders with calcification, 14 were in men and 41 in women. In brief, 25 per cent of women had calcific rotator cuff deposits, but only 15 per cent of the men. Our findings would tend to refute general orthopedic opinion that calcification occurs on a degenerative basis associated with the wear and tear of daily repeated traumata.[1,2] Thus one would anticipate a greater prevalence in men, because of their greater physical activity. Bosworth found the incidence of calcium deposits to be 3.6 per cent in men and 2.5 per cent in women.[1] Without doubt, degenerative changes are more striking elsewhere in the musculoskeletal system in men.

One would also anticipate a greater incidence of calcification on the dominant side if wear and tear were the prime factors. However, of 35 patients with one shoulder showing calcific change, 18 showed changes on the dominant side and 17 did not—a rather striking equality for such a small group. Also refuting this thesis of wear and tear is the fact that the many persons doing the heaviest type of work showed no calcification. Of 38 people doing heavy work who showed calcification in one or both shoulders, 22 had calcification on the dominant side and 16 on the nondominant side. Of 17 in light occupations, 7 showed calcification on the dominant and 10 on the nondominant side.

Pain

A question often asked is whether the calcific deposit has any clinical significance. Is it the pain producer? Our feeling is that the calcium deposit is purely incidental when confined to the tendon, but, when it invades the subacromial bursa, it acts as an irritant and produces an acute inflammatory reaction. It takes on a fuzzy, ill-defined appearance on

All four authors are members of the staff of Albert Einstein Medical Center, Northern Division, Philadelphia—SEYMOUR M. ALBERT *as associate orthopedist;* DAVID MANN SKLAROFF, *associate radiologist;* ABRAHAM M. RECHTMAN, *chief of orthopedics; and* HAROLD SCHRAER, *research biochemist.*

roentgenogram and is significant. The sharply defined, dense, well-organized deposit is old, quiescent, confined to tendon, and it causes no symptoms.

This opinion has been propounded by McLaughlin[3] and we believe it is shared by most orthopedists. We also believe that the recurrent episodes may be caused by recurrent invasions of the bursa, although others may disagree.[4]

Of the 55 shoulders which showed evidence of calcific deposit, only 9 had pain. There were 16 shoulders in the series that were painful and had no deposits. Of the 16, 6 had degenerative changes in the acromioclavicular joint; 5 in the area around the greater tuberosity; 2 in the region around the acromium, which itself showed roughening; and 3 showed changes in the shoulder joint. The significance of these changes must be questioned also, since 46 shoulders showed similar pathology and were asymptomatic. There were 17 painful shoulders that were negative roentgenographically. Fifteen shoulders showed evidence of calcification and other changes either about the tuberosity, acromioclavicular joint, or shoulder joint, yet were free of symptoms.

Based on these statistics, we might consider the presence of calcium about the rotator cuff as significant. While the series is admittedly small, pain was present in 9 out of 55, or 16 per cent, of those shoulders with calcific deposition, and in 17 out of 195, or 8 per cent, of those roentgenographically negative. However, if one includes the 16 shoulders which were painful, showed evidence of degenerative phenomena about the shoulder girdle, but no calcification, the resulting figure of approximately 16 per cent is strikingly similar to the calcific group. Basing our statistics solely on the presence or absence of calcification, incidence of pain was notably similar.

Motion

Grating on motion was noted in 19 shoulders with calcification, or 34.5 per cent, and in 65 shoulders without deposit, or 33.3 per cent, suggesting lack of any correlation between grating and calcification. Restriction of motion was evaluated in forward flexion and internal rotation behind the back for, when restriction was present, these two planes almost invariably showed the greatest restriction. A minimum normal was considered to be 170 degrees of forward flexion and internal rotation to the lower angle of the opposite scapula. With calcification, 24, or 43 per cent, showed some restriction, compared with 90, or 46 per cent, of those without calcification. This finding would suggest that an inert or relatively inert deposit does not affect motion. It was also interesting to note that, of 35 patients who had only a unilateral deposit, motion was better on the calcified side in 21, on the noncalcified side in 6, and showed no significant difference in the other 8.

Trauma

We attempted to evaluate the significance of previous acute trauma, such as fracture, to the upper extremity in the production of a deposit. Of 26 patients with such a history, only 5 had deposits in the involved extremity. This series seems a bit too small to draw any conclusions. However, it did suggest that an acute, gross trauma had little if any significance, for the percentile evaluation closely approximated that of the entire series—19 as against 22 per cent—and was actually less.

From the Orthopedic and X-ray Services, Home for the Jewish Aged, and Albert Einstein Medical Center, Philadelphia, Pennsylvania.

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Response potentials of vascular tissues and the genesis of arteriosclerosis—a review

Part I. The concept

HERMAN T. BLUMENTHAL, Ph.D., M.D.
ST. LOUIS, MISSOURI

If arteriosclerosis is regarded as a complex mixture of degenerative and reparative processes leading to increased rigidity, diminished elasticity, and decreased caliber of arteries, then the development and characteristics of the lesion are dependent upon these tissue response potentials. This first article presents the pattern of such responses for endothelium, collagen, elastic tissue, muscle, and the vasa vasorum. A second article, to appear in later issues, will review the factors involved in the etiology of arteriosclerosis.

◆Although nearly a century has passed since Virchow first described the gross and microscopic characteristics of arteriosclerosis and from these developed a theory of pathogenesis,[1] it is still necessary to remind ourselves periodically of some of the fundamental characteristics of this disease. Emphasis on certain aspects of the disease process to the exclusion of others because of momentary discoveries leads to a loss of perspective. As Hass points out, arteriosclerosis "may be regarded as a complex mixture of degenerative and reparative processes which lead to increased rigidity, diminished elasticity, and often decreased caliber of arteries."[2] In the most common form, there are often accentuated focal points, but with a tendency to spread and become confluent. At times the process involves only local vascular segments or certain branches of an organ system. In most cases, however, there is a general pattern of gross distribution and microscopic characteristics of lesions. While our own studies disagree in certain details with the accepted distinctions between lesions in elastic and muscular arteries, as well as in small intraparenchymal arteries,[3-9] the fact remains that, in aged individuals, all of these segments are usually involved and differ in certain microscopic characteristics. Because intensity of different arterial segments varies from case to case, the overall pattern is often neglected.

Furthermore, from the standpoint of susceptibility, the distinction between normal health and arteriosclerotic disease is more quantitative than qualitative.[10] In a series of 1,200 consecutive autopsies of adults dead from all causes in Minnesota, Keys and Anderson[10] found some degree of sclerosis of the coronary arteries to be almost universal. Incidence of noticeable arteriosclerosis was 73 per cent among men and 61 per cent among women in the age group of 50 to 60.

During the decades since Virchow, many theories have evolved as to the etiology of arteriosclerosis. These con-

HERMAN T. BLUMENTHAL *is director of the Division of Laboratories, The Jewish Hospital, St. Louis, and associate professor of pathology, St. Louis University School of Medicine.*

cepts may be placed in three general categories: (1) *the inflammatory theory*, which holds that arteriosclerosis is the end result of the response of inflammatory processes; (2) *the lipid metabolic theory*, which supports the concept that metabolic disturbances primarily involving lipids lead to the development of atherosclerotic plaques; and (3) *the mechanical theory*, which holds that arteriosclerosis is the end result of the response of vascular tissues to hemodynamic forces exerted over long periods.

Each of these lines of investigation has achieved popularity, but with an almost complete exclusion of certain basic considerations established in the others. New definitions and terminology have been introduced, resulting in considerable confusion. For example, current medical literature is replete with such terms as arteriosclerosis, atheromatosis, atherosclerosis, Monckeberg's medial sclerosis, hyperplastic sclerosis, and so on, without clear-cut distinctions as to where they differ from each other and where they overlap.

Some investigators have attempted a synthesis of these various etiologic concepts. Chief among these is Hueper's theory of "anoxemia"[11] in which he postulates that, whichever of the causal agents and mechanisms affects the arterial wall, the end result is an interference with the oxidative metabolism and nutrition of the wall. Such a concept emphasizes certain biochemical aspects of pathogenesis and minimizes the importance of preceding causal events. Rather than placing emphasis on syntheses of this type, it seems to us that each concept has an area of validity and that what is required is sharper delineation and establishment of criteria regarding zones of applicability.

This ferreting out of etiology on the basis of final microscopic characteristics may be compared with a similar problem in the glomerulus of the kidney, in which complete hyalinization represents the end stage, whether the lesion has developed on the basis of nephrosclerosis, chronic glomerulonephritis, or chronic pyelonephritis. Thus, in the arterial system, the final lesion in any particular anatomic site may be similar whether it develops from inflammation, from primary lipid deposition, or by wear and tear with compensatory changes. As Waters points out, the "conception of the uniformity of vascular response to injury is fortified by the fact that injury by physical agents as well as by chemical or infectious ones results in the same basic response."[12] Increased intravascular pressures produced experimentally in animals result in acute arterial changes similar to those occurring in human hypertension, and which are often indistinguishable from those that follow chemicals, bacteria, or the hypersensitive state.

Fundamental to an understanding of the pathogenesis of degenerative arterial disease is the fact that the various histologic components of the arterial wall are capable of a definable range of responses to a variety of injurious agents. Range and pattern of such responses are dependent upon the variety of tissues present in a particular artery, the quantities of each, and their arrangement within the arterial wall. Also important is the intensity with which the agent is applied. All arteries consist of a lining endothelium, connective tissue, collagen, elastic tissue, intercellular ground substance, and smooth muscle, and certain arteries also contain an intramural vascular supply. These components differ in their susceptibility to damage and their ability to regenerate.

It is also evident that differences in quantity and distribution of these elements in various sites are already present at birth. Such differences may be the result of hemodynamic factors operating in the embryo. These also vary with anatomic location and may influence the development and distribution of tissue

components. If we are to judge from the effects of hemodynamic forces in adult arteries in which growth potential is considerably less than in the embryo, this is a distinct possibility. It is supported also by reports by several observers of calcification of coronary arteries of infants.[13-15]

The purpose of this paper is to develop the concept that the characteristics of the arteriosclerotic lesion are determined primarily by the range of tissue responses of which the artery is capable, rather than by the nature of the etiologic agent. Accordingly, we shall first examine the response capabilities of each arterial component and how they are affected by and respond to various injurious agents.

The Endothelium

The endothelial lining of blood and lymph channels is usually designated common endothelium to distinguish it from the more specialized reticuloendothelial cells. It is generally considered to consist of a single layer of flattened cells, whose main function is to provide a smooth gliding surface for the flowing blood stream. It also serves as a membrane through which nutrients gain entrance to underlying tissues and waste products from the tissues are discharged into the blood. It may also serve as a protective barrier against any injurious agents present in the circulation.

The form of these cells is thought to be determined by the functional state of the vessel wall and by influence from neighboring tissues.[16] Age may have an influence on size and shape of endothelial cells in that they become progressively flatter.[17] It was observed recently that the endothelium of arteries of infants is composed of slightly elongated, large polygonal cells of extreme thinness, oriented in the direction of the long axis of the artery.[18] Initially uniform and regular, by the age of 8 years they begin to show irregularities and, with advancing years, become symmetrically polygonal. Concomitantly, there is a loss of longitudinal orientation and variations in size and shape appear. Some cells become quite large and multinucleated. These changes are most pronounced in large vessels and less so in smaller arteries. They are progressive up to about age 60 after which little change is noted.

Several observations indicate an influence of mechanical factors on these alterations. The preferential distribution in large arteries may possibly be a response to gradual dilatation of arteries with age.[19] Binucleated cells have been observed, especially at orifices where the changing direction of flow of the blood stream results in an action of injurious mechanical factors.[20-22] It is believed that such alterations may represent a reaction to special demands.[23] These alterations would fit in with others which we have described as responses to hydrostatic tension.[8,9]

Because of its exposed location, the endothelial lining is vulnerable to injury, and an understanding of its regenerative capacity therefore assumes importance. While outgrowing capillaries in reparative processes commonly show mitoses, Altschul[16] and Kuntz and Sulkin[24] could find only amitotic divisions in endothelial cells of arteries involved in experimentally produced atheromatous plaques. According to Stchelkounoff, damaged surface endothelial cells are replaced by undifferentiated cells in the underlying intima, and the latter may show mitotic activity.[25] Altschul's excellent monograph presents evidence that, except possibly in actively proliferating granulation tissue, endothelial cells lack the potentiality for undergoing mitotic activity, and are thus to be considered fully differentiated cells.[16] On the other hand, certain investigators contend that such cells can dedifferentiate into multipotent cells and form other vascular components. Some workers contend that the latter concept is supported by the

fact that the earliest vascular structures in embryonic life consist of an endothelial tube from which other vascular components may be derived. However, it appears more likely that totipotent cells exist in the subendothelial layer of even adult arteries[25-27,19] and that such cells, under proper stimulus, may replace endothelium or differentiate into other vascular tissue components. This concept will receive further attention in connection with other vascular elements.

The ability of the endothelium to regenerate is of particular importance in the prevention of thrombosis, since Brücke[28] and many others have ascribed damage to endothelium as a prime factor leading to this complication. Many subsequent investigators believe that damage to the endothelium causes a roughening of the inner surface, facilitating the deposition of platelets and fibrin.[29-31,1] There is, however, some evidence that injury to endothelium may not be critical, since large ulcerated plaques may show no thrombosis while extensive fresh thrombus may be present over an intact endothelial surface.[29] It is also asserted that endothelial damage has little if any influence on thrombogenesis, except in traumatic thrombosis or otherwise diseased vessels.[32,30] Stuber believes that diminution in rapidity of blood flow is a more critical factor than endothelial injury in causing thrombosis.[33]

Another important consideration is the role of the endothelium in providing nutrients to the inner portion of the artery wall. Most observers believe that this is brought about by diffusion from the blood stream.[34-36] There are, however, local variations in permeability. Okunoff maintains that those areas of blood vessels which are most susceptible to arteriosclerosis have, even under normal conditions, a greater permeability than other parts of the vessel.[37] Endothelial permeability is reported as greater in the abdominal aorta than in the thoracic segment or arch.[38] Permeability also varies with age, according to Wendt, who observed a progressive rise to the twentieth year, followed by a plateau until the fiftieth year, after which it declined.[39] He also noted that the diffusion of water, sugar, and oxygen parallels the curve of blood pressure, an observation confirmed by Hackel.[40] All of these observations may represent physiologic expressions of the morphologic changes noted by Lautsch and Rotan[18] as well as reactions to hemodynamic forces. Permeability may be increased by inflammatory reaction to the extent that chylomicrons and smaller lipoprotein particles may gain entrance through the endothelium.[12] Apparently they are unable to pass through normal intact endothelial cells.

Still other workers maintain that there are definitive intercellular gaps in the endothelial membrane.[41,42] They explain the formation of such spaces on the basis of transient enlargements of intercellular substance, particularly in inflammatory states and circulatory disorders, and this may represent the mechanism of increased permeability alluded to by Waters. A more or less permanent loose arrangement of endothelial cells of the aorta has been observed[43] and it is reported that gaps develop temporarily by a liquefaction of cytoplasm in the cement substance or basement membrane.[44] Still other investigators completely reject the evidence for the existence of definitive endothelial stomata.[45-48,34]

Winternitz, Thomas, and LeCompte, using injection technics, have demonstrated stomata which communicate with the lumen as well as with intramural plexuses of vascular channels originating from vasa vasorum;[49] these should be considered as ostia of definitive vascular channels and would therefore play no role in processes of diffusion.

The arrangement of endothelial cells is also of particular significance because of observations that the intercellular substance is more permeable than the cells

proper.[50] In view of the possible loose arrangement of endothelial cells, expansion and contraction of the artery wall may provide a mechanism for increasing and decreasing intercellular spaces, thus resulting in a rhythmic flow of nutrients into the vascular wall. While most studies on contractility have dealt with capillaries,[50-52,36] observations in arteries are extremely difficult to interpret because of the independent contractility and elasticity of other components of the wall. The endothelial cells are said to have little influence on contractility and elasticity of arteries, but they may have independent contractility which may also influence passage of substances in and out of the wall.[53] Nevertheless, many investigators[54-57,31] believe that repeated insults to the endothelium in the form of infectious agents or toxins disturb endothelial permeability without necessarily producing intercellular spaces, so that the subendothelial tissues become the seat of edema which may subsequently result in the deposition of lipids and calcium.

In addition to matters of permeability, there is evidence that the endothelium may actively secrete,[58-63,30,32] but others reject such a concept.[62,63,32] Borst believes that the endothelium may secrete, but only under pathologic conditions.[64] Lack of clotting in capillaries in burns and other conditions suggests that these cells may secrete a fibrinolysin. These observations on the state of endothelial preservation and its role in the prevention of fibrin deposition assume special importance in Duguid's concept that intimal plaques are the result of a progressive deposition and organization of fibrin deposited on the endothelial surface.[65]

Finally, there remains the problem of phagocytic ability of endothelial cells, the proof of which must rest on a demonstration of active movement of cells as well as active engulfment of particulate matter. Thus, while Stilwell reports passive phagocytosis,[66] Silberberg believes that carbon particles pass through the endothelium without participation or alteration of the latter, and that such particulate matter is subsequently picked up by adjacent phagocytes.[67] This function is particularly important in considering the mechanism by which lipids appear in the artery wall. Lipophagia by endothelium is thought to be an expression of a decrease in vitality, in which fatty substances may result from an intracellular decomposition or may be transferred from the outside into the cell which can no longer repel them.[68] The acceptance of thorium by the endothelium during atherogenesis in the rabbit may represent a process of the latter type, since normal endothelial cells are impermeable to Thorotrast.[69] In any event, it is doubtful that this is true phagocytosis. According to Aschoff and Kyono, whenever the circulation becomes overloaded with a particular substance which can be resorbed, the endothelial cells of many blood vessels take up small amounts, and in some areas as in intestinal villi, they may even detach and turn into histiocytes.[70] Common endothelium and fibroblasts have such a property for storing and may subsequently even show active movement. Others believe that this may apply in the formation of atheromata in hypercholesterolemic states.[68,16] Several investigators have described the transformation of endothelial cells into foam cells,[71-75,11,16] but this process has been denied by others[76-78] and accepted only as an occasional process of little significance by Duff.[69] Palade recently advanced a hypothesis postulating that the mechanism of fluid transport consists of an active bulk secretion by the process of pinocytosis commonly observed in tissue culture cells, in which small volumes of the medium are engulfed and transported through the cell cytoplasm.[79]

Thus, by its vulnerable position, the endothelial membrane is subject not only

to physical stress but to changes in chemical environment. The response to physical stress over long periods appears to result in changes in the size and shape of the cells. When cells are injured, regenerative processes occur, but there appear to be limitations in what the mature endothelium can perform, with replacement, for the most part, taking place by proliferation of undifferentiated subendothelial cells. Nutrition of the inner part of the vessel wall appears to be primarily by diffusion through the endothelial membrane, but physical stress, inflammation, and probably changes in the chemical constitution of the circulating blood all alter permeability. Endothelium appears to be impermeable to chylomicrons and lipoproteins under normal conditions, but may be made permeable by factors which increase the intercellular spaces. Definitive endothelial stomata are probably not present in normal membrane, but develop as the intima thickens and intramural vascular channels are formed. Under pathologic conditions, endothelial cells may develop phagocytic ability, which appears to be lacking under normal conditions. Needing considerable further study is the question of whether endothelium secretes, since such a mechanism would afford protection against precipitation of fibrin, a process by which atheromatous plaques may develop.

Nonelastic Components of the Intima

The source of ground substance, collagen, and reticular fibers, the principal components of the intima, is important to the embryologist and to the pathologist, since the pathologic development may be related in its mechanical pattern to embryonic development and may closely mimic the latter. Since the earliest recognizable vascular tube consists of a single layer of endothelial cells, it is natural to assume that the other components of the vessel wall are derived from these cells. The reticular fibrils, collagen, and possibly even muscle and elastica may be derived from endothelium,[43,16] and Schaffer believes that all components of the artery wall except the adventitia are derived from this tissue.[80] More widely accepted is the concept that all layers except the inner lining develop from perivascular mesenchyme.[81,82]

Aside from the endothelial basement membrane, there appears to be no definitive intimal layer in arteries of the newborn with the exception of those vessels which disappear shortly after birth, although occasional isolated fusiform cells may be identified between the endothelium and the elastica interna. According to Benninghoff,[23] Chrozonszczewsky was the first to recognize a basement membrane for the endothelial layer, although no information is available as to when this structure first appears.[83] Benninghoff believes that this membrane is continuous with the elastica interna and invests the elastic lamella. Zimmerman shares this view, and also believes that the basement line corresponds to the basal fringes of the endothelium of smaller vessels.[84] This subendothelial structure is most conspicuous in capillaries, is periodic acid - Schiff positive, and may therefore contain mucopolysaccharide. It may represent the initial appearance of ground substance which precedes collagen formation, or it may represent a component part of the elastica interna, in which case the latter may be the source of earliest appearance of ground substance.

The subendothelial matrix containing scattered fusiform cells has been called the "cambium."[25] Thoma stated that this cambium is lacking in the fetus and develops only after birth.[27] Prior to this, Langhans described subendothelial cells which he believed to be related to, but not descended directly from the endothelium. Like Thoma, he did not find them in the embryo nor was he able to

identify them before the tenth year of life.[26] Others have described this cell type and considered it to have features transitional between smooth muscle cells and fibroblasts.[85-87,26] Duff believes that such cells are present even in childhood, and that they can be visualized by sections taken along a surface parallel to the plane of the endothelial membrane.[19] He describes such cells as having an oval nucleus, flattened cytoplasm of variable size and a stellate outline with numerous branching processes, all of which lie in the curved plane of the subendothelial space.

The morphologic differences between fibroblasts, mesenchymal cells, and endothelium are slight. Some authors think that the possibility of a cell in the normal mesenchymal spongework of the embryo becoming an endothelial cell depends merely on whether it comes to line blood or lymph spaces in the mesenchymal spongework.[88-90,57] Such opinions, however, do not resolve the problem of the potentialities of differentiated endothelial lining cells discussed in the preceding section. Some investigators have reported the transformation of endothelium into fibroblasts,[91-94,20-22] a view which is not accepted by Marchand[95] or by Silberberg.[67] Toro believes that fibroblasts which may develop from endothelium are not identical with the common connective tissue cell, but that they may have a specialized function.[96]

As the intima grows, the most prominent element which appears is collagen. According to Moon and Rinehart there is first a deposition of mucopolysaccharide-containing ground substance and proliferation of fibroblasts, followed by a laying down of collagen fibers.[97] On the other hand, Altschul believes that, through metaplasia, endothelial cells may dedifferentiate and form collagen.[16] Historically, two theories have been proposed for the formation of collage: (1) that a cortical layer of connective tissue cells is transformed into intercellular substance, and (2) that the intercellular substance is a secretory product of the connective tissue cell.[98] From the standpoint of the development of intimal collage, it would be difficult to accept either theory, because of the rarity of fibroblasts in this layer during the first decades of life, and the subsequent disproportion between numbers of fibroblasts and quantity of collagen. Schwann[99] and Henle[100] have proposed still a third concept—that deposition of intercellular substances occurs independently of connective tissue cells—which would conform more with the observations of Moon and Rinehart.[97] Other studies indicate that fibrin may be transformed into collagen fibers without the interaction of fibroblasts.[101-106] It was recently demonstrated that, through the interaction of procollagen and plasma mucoprotein, collagen fibers are produced.[107] Duguid believes that intima and also plaques are built up by a progressive deposition of fibrin along vascular walls which then becomes transformed into collagen and covered over by endothelium. At least a contributory role for fibroblasts should be considered, since Porter stated that fibroblasts cultured in protein free media can form collagen fibers, but that such fiber formation is accelerated by the addition of plasma.[108]

Especially pertinent to the immediate subject is the response of fibroblasts and collagenous elements in the intima to injury. Taylor showed that, in rabbits, the proliferative capacity of these intimal elements diminishes with age, and that lipid deposits in the intima may further retard these processes. Instead, such deposits appear to stimulate formation of a hyaline fibrous connective tissue.[109] Rabbit aorta rendered necrotic by freezing is repaired by a proliferative response restricted to the intima. This consists of a proliferation of fibroblasts, followed by the formation of collagen and elastic fibers, and new formation of smooth muscle.

Baumgarten described formation of granulation tissue in ligated vessels which appeared to arise from endothelium.[91] He concluded that the endothelium in ligated vessels becomes the matrix for a new cellular primordium. Rotter has likened these changes to endarteritis obliterans, or to the postnatal obliteration of vessels, but he differentiates this reaction from inflammatory endarteritis in which the outer coats also play an important role.[56] Thus blood stasis alone may stimulate the formation of granulation tissue. On the other hand, inflammatory agents may cause a similar arteritic process which, in later stages, proceeds to the formation of collagen. In such instances there are also responses of smooth muscle, elastic elements, and vascular components as will be discussed in later sections.

Contrary to the general opinion that the primary deposition of lipids in the artery wall is followed by fibroblastic proliferation and deposition of collagen, newer evidence indicates that lipids may actually retard this process and call forth instead a hyalinization of existing fibrous elements.

Furthermore, it is not generally recognized that mechanical factors may play a role in collagen deposition. Von Ebner observes that collagen fibers can develop from a colloidal medium under the influence of mechanical forces.[101] Nageotte demonstrated that such fibers can also be precipitated from a cell and fiber-free acid solution of collagen by the addition of salts,[103] an observation confirmed and expanded by Huzella, who showed that fiber formation from a homogenous solution of collagen is under the exclusive control of physicochemical forces.[110] These workers succeeded in producing fiber frameworks whose architecture simulated that of various organs and tissues of the living organism.

Almost any kind of injury to the walls of arteries is followed by a proliferative response in the intima.[19] This is true even when there is no evidence of actual destruction of any of the elements of the artery wall, although evidence of injury may be present in the form of an inflammatory reaction. Apparently, weakening of the elastic and muscular components with stretching of the artery can stimulate intimal proliferation. Thoma believes that the primary factor is the weakening and stretching of the wall,[111] but Duff points out the possibility that the same injurious agent which damages elastic and muscular components may at the same time stimulate intimal proliferation. This proliferative tendency of the intima is a most important response, since, in any well developed lesion which encroaches on the lumen, there is at least as much fibrous tissue as lipids and, in many instances, the latter form a relatively small component. The fact that the intima is not a definitive layer at birth but develops progressively indicates that this is the basic intimal response. Other responses to injury are probably superimposed and contribute to the loss of tensile strength of the artery wall. The first stage is most likely to be a deposition of sulfated mucoproteins followed by a deposition of collagen fibers.

Elastic Tissue

Our lack of information regarding the embryonic development of elastic fibers hampers our understanding of the mechanisms of elastic tissue synthesis occurring after birth. Until recently, it was assumed that the elastoblast, a specific subendothelial cell, was responsible for the synthesis of elastic fibers. Altschul believes that through metaplasia, endothelial cells may dedifferentiate and form collagen as well as elastic tissue.[16] If endothelial cells are made to proliferate, as in ligated arteries or in arteriosclerosis, elastic fibrils appear between them and these fibrils often show no connection with the old elastic tissue. On the other

hand, Jores does not believe that endothelium can form either collagen or elastic fibers.[112]

At suture sites of arterial wounds, the internal elastic lamina does not reform, but delicate elastic fibrils grow into the scar and into the granulation tissue beneath the endothelium.[113] At the proximal and distal anastomoses in autogenous grafts, intimal thickening appears, largely caused by an increase of elastic fibers. In homografts, the intima sloughs, leaving the internal elastic lamina exposed to the blood stream; fibrin deposits are organized at this site, and new elastic filaments are formed. In studies of devitalization of the arterial wall by transmural freezing, it was noted that, within the devitalized shell of residual fibroelastic tissue, there was little regenerative activity, but the overlying intimal cells underwent progressive proliferation and differentiation, and a new vascular wall was constructed with new elastic elements.[114,115] Simple piercing of the intima of the rabbit aorta with a needle inserted at an oblique angle results in a localized fibroelastic thickening similar to the fibroelastic cushion in infants which some believe to be the precursor of the adult atheromatous lesion.[116]

Recent reports indicate the possibility that the elastic fibers may develop from collagenous elements, although real proof for such a concept is still forthcoming. The possibility that collagen fibrils actually form an integral part of certain natural elastic structures has been considered.[117,118] More recently, on the basis of certain experimental observations, a scheme was proposed in which protein and polysaccharide precursors in ground substance undergo a series of synthetic reactions in the direction of formation of collagen fibers on the one hand and elastic fibers on the other.[119] In addition, collagenic units either in varying degrees of organization or of degradation may also be converted to elastic fibers. It has been suggested that an enzyme, elastase, first reported by Balo and Banga,[120] may play a role in both degradation of elastin and in its synthesis from collagenous precursors. Some evidence to support this has been obtained in our own laboratories.[121] Such processes may account for postnatal responses to injury, but the embryologic development of elastic membranes does not appear to be related to collagen formation.

Recent evidence may indicate a relationship between collagen and elastin.[122] "Elastotically degenerated" fibers are described, which are believed to be formed either by degeneration of pre-existing collagen or as a result of metabolic disturbances leading to collagen or reticulin fiber deposition. This material may be similar to elacin, collacin, and collastin described by Unna many years ago.[123] Such conclusions are based on the observation that, while true elastic tissue will stain with all recognized elastic fiber stains, the "elastotically degenerated" material will stain only with certain ones. In addition, it will take up dyes which do not stain elastic membranes. It is possible the altered staining affinities may represent either incomplete forms of elastic filaments or partially degraded old elastic elements.

Within the artery wall, the media lies between the internal and external elastic lamella. In the aorta and segments of transitional branches, the media also contains multiple concentric elastic membranes. The internal elastic lamella lying between intima and media may constitute a blood-media barrier and may have something to do with discriminating between materials which pass back and forth between the avascular media and the blood stream. Some believe that the internal elastic membrane consists of an interlacing pattern of fibers and such materials may pass between the apertures. The size of such interstices would depend in part upon the state of expansion or contraction of the artery

wall. The passage of substances may be rhythmic, as suggested also regarding the spaces between endothelial cells.

In degenerative vascular disease, as in human arteriosclerosis, the elastic fibers increase in rigidity through calcification; they break into fragments and may become encased in fibrous splints.[124] These alterations are accompanied by thickening of the overlying intima and degenerative changes in the underlying media. Hass believes that the loss of chemical and structural integrity of the internal elastic membrane and of the underlying media may be one of the significant events in the pathogenesis of arteriosclerosis. Duff believes that the intimal reaction may represent a response to stretching resulting from loss of elasticity incurred by these degenerative processes,[19] but Waters points out that such phenomena are also accompanied by condensation and hypertrophy of underlying elastic fibers.[12] In muscular arteries, the response may consist in a reduplication of the internal elastic lamella as well as new formation of intimal and medial elastic fibers. In aged arteries, elastic tissue degenerates to small fibrils and even granules, some of which may represent the "elastotically degenerated material" just described.[122]

Lansing has shown that, although the quantity of elastin in the media and pulmonary artery does not change with age, yet its chemical composition in the aorta does so.[125] He reports a thirty-fold increase in calcium accompanied by an approximate doubling of each of the dicarboxylic amino acids, aspartic and glutamic.

One of the most profound alterations in all degenerative vascular disease is loss of tensile strength. The elastic properties of the aorta in relation to age have been quantitatively measured in human material by Wilens[126] and in material from the rabbit by Saxton.[127] In my own studies, I have found that the most striking change is a calcification of the elastic fiber, along with reduplication and the appearance of filaments and granules of elastic and pseudoelastic materials. Despite these changes, Hass accounts for the loss in tensile strength on the basis of transverse fractures in elastic networks and the progressive development of fibrous tissue which splints the elastic tissue in an overextended state.[124] He has observed that, when the fibrous tissue is extracted by chemical methods, the elastic tissue retracts and the vessels return to normal dimensions. This conclusion may be valid insofar as the connective tissue extraction also leads to decalcification of the elastic fiber, since the deposition of calcium is the probable cause of the rigidity and brittle state predisposing to fractures. But it does not take into account the fact that newly formed elastic elements may also play a role in the reconstitution of the tensile strength of the artery wall.

It thus appears that the earliest evidence of intimal thickening is the appearance of sulfated mucopolysaccharide containing ground substance. Such material is present in the basement membrane of the endothelium which Benninghoff believes is continuous with the internal elastic membrane.[23] Such mucoproteins also appear to constitute the matrix of the elastic fiber.[128,129] Within this matrix, the fibers seem to be intertwined much like rope cords. In 1950, Balo and Banga discovered elastase, an enzyme extractable from pancreatic tissue, which causes these fibers to uncoil and separate.[120] This reaction probably represents the first stage of degeneration of the elastic lamella. This reaction is believed to release lipids, but this observation is subject to the criticism that the enzyme preparation as well as the substrate may have contained lipid impurities. Nevertheless, most investigators now agree that the action of elastase is that of a mucase, and more recent studies indicate that denatured collagen may also be dissolved by elastase.[119]

Thus it appears that enzymatic reactions, as well as mechanical and other injurious agents, may cause degenerative changes in elastic elements with the release of mucoproteins. The possibility that mechanical factors may initiate biochemical reactions is almost completely unexplored. Such studies appear necessary to determine whether there is any relation between mechanical effects on vascular structures and the apparently related biochemical processes. While some investigators believe these changes are coincidental with progressive intimal thickening, there is as yet no proof that they precede and stimulate the deposition of intimal collagen and elastic fibrils. At any rate, these are the earliest changes in the formation of intimal plaques.

With progressive degeneration of the elastic fiber, there is also a progressive deposition of calcium either on the surface or within the substance of the elastic elements,[3-9] and this appears to be the major source of calcification within atheromatous plaques. Although it has not yet been established whether the source of lipids is endogenous or exogenous, the new formation of elastic fibrils appears to be inhibited by the presence of lipids. These observations are of particular importance, for in animals made hyperlipemic, who show primary atheromatosis, there is no apparent tendency for such plaques to calcify and ulcerate, and the thrombotic complications common in human subjects are extremely rare under experimental conditions.

Smooth Muscle

Unlike the heart, which lacks the capacity to regenerate muscle fibers, the arterial wall seems to retain mechanisms for reconstitution of smooth muscle. Baumgarten first described the formation of granulation tissue in ligated vessels, apparently from endothelium, and described smooth muscle cells and fibroblasts in this proliferating tissue.[91] Huebner reported transformation of endothelium into smooth muscle in syphilitic vascular disease.[130] More recently, Taylor observed cells from the proliferative intima assuming the characteristics of smooth muscle at sites of injury by various physical agents.[109]

The reactive capabilities of smooth muscle have been studied less than the other tissue components of the artery wall. One point which appears to have been overlooked is the development of smooth muscle fibers in the intima. As the intima thickens, smooth muscle fibers appear in the intimal layer, and, in some arteries such as the coronary, become quite conspicuous. The best assumption is that these fibers come from scattered, undifferentiated, subendothelial fibroblasts, although certain reports indicate that lining endothelial cells dedifferentiate and migrate into the intima and then differentiate into smooth muscle.[16] Other investigators account for the appearance of smooth muscle fibers in the intima on the basis of migration from the media.

The regeneration of smooth muscle cells of the media proceeds slowly and only under favorable conditions. The muscle cells of the media will grow into an area of injury only if the elastic framework remains intact, forming a scaffold for the orientation of such fibers.[131] However, it appears that, in human subjects, optimal conditions for such regeneration are rare. Further, since the formation of elastic elements does not usually reproduce the original elastic framework, regenerated smooth muscle may also lack proper orientation. While minute injuries that are not associated with much disturbance of the general architecture may be expected to lend themselves readily to regenerative repair, grosser defects are replaced mainly by scar tissue.

Epinephrine has been shown to have injurious effects on medial muscle.[132,133] Among such changes are necrosis, calcification, and eventual replacement by

fibrous tissue. A greater increase in incidence and intensity of medial necrosis was demonstrated when thyroxine is added to the administration of epinephrine.[134] Spontaneous lesions of this type have been reported in the rabbit[135] and we have observed late stages with calcification, particularly in the human splenic and renal arteries[6] as well as in those of the lower extremities.[8] This process, in part, accounts for the development of Monckeberg sclerosis, although calcification of elastic fibers may be equally as intense.

The role of hemodynamic factors in medial injury was assessed by injections of vasopressor substances into animals.[12] With certain pressor amines, inflammatory lesions were obtained as well as arteriolar necroses following acute hypertensive episodes. Similar effects were observed with renin. It was concluded that these effects were due to hemodynamic factors since pretreatment with Dibenamine abolished the effects of adrenalin. Interestingly, the favored sites for the development of lesions are at points of exit of branches of the aorta, thus corresponding to the usual foci for human arteriosclerosis. The role of prolonged vasoconstriction, of changed distribution of blood in the organs, of hypoxia, and possibly of other factors is still to be evaluated.

As to the role of hemodynamic factors, large vessels, such as the aorta and pulmonary arteries, are dilated during acute epinephrine hypertension. On the other hand, there is generalized constriction of the arterioles of skin and mucous membranes, and these show no lesions. It is important to know whether the vessels which suffer necrosis are dilated, constricted, or of normal caliber. It is possible that vessels with less thick muscular walls may be dilated when the increased intraluminal pressure imposed on the wall is greater than the maximum potential constricting force possessed by the muscular coat. The lack of basic knowledge as to the metabolism of smooth muscle of the vessel wall makes impossible the evaluation of these observations at the present time. It should be pointed out that these observations deal with a relatively acute situation in using vasoconstrictor drugs, whereas, in human arteries, such lesions appear even in nonhypertensive subjects, presumably on the basis of repeated periodic elevations in blood pressure.

It appears that hemodynamic factors are also important in injury to smooth muscle and may be potentiated by certain hormonal factors. These are relatively acute processes, followed by fibrosis and calcification. They are common lesions in those human arteries which are known to be strong constrictors under the influence of norepinephrine. Smooth muscle cells also may be destroyed in inflammatory vascular processes, the most prominent of which are syphilitic and rheumatic vascular disease. Regeneration of smooth muscle may occur, but only to a limited extent and when injury is trivial. Injury to this vascular component usually results in necrosis, calcification, and replacement by fibrous tissue. However, smooth muscle cells may appear in the progressively thickening intima, possibly representing a more prolonged, gradual response to hemodynamic factors.

Intramural Blood Supply

Certain tissues are able to function without any blood supply. Among these are cartilage encased in an endochondral membrane, lens of the eye, the cortex of the tooth beyond the pulp canal, as well as the middle third of the artery wall, at least during certain periods of life. The permeabilities of such tissues are therefore important in their survival as are also such influences as spreading factor and the various hormones in the diffusion of nutrients.

Two additional possible sources of nutrition to the vessel wall have been point-

ed out—the vasa vasorum and a hypothetical mural canal system.[136] According to Winternitz, the "ramifications of the adventitial vasa within the media anastomose freely with complementary vessels arising at the mouths of large branches, and also independently from the lumen of the mother artery."[137]

Such plexuses of vessels are prominent in cattle, horses, and sheep, but are far less conspicuous in man and smaller mammals. The arterioles contributing to the mural plexus arising from the lumen of the mother vessel are rarely found in man when there is no other expression of vascular adjustment.[137] Vascular channels arising from the intimal surface of the canine aorta and the normal canine and human coronary artery are extremely rare.[318] However, the vascular plexuses become greatly exaggerated in man with increasing age and especially with thickening of the arterial wall and narrowing of the lumen. The problem may be one of demonstration rather than existence, but if this is the case, it is nevertheless evident that such channels play only a minor role in the nutrition of the inner part of the wall in the early decades of life when mechanisms for diffusion, comparable to those noted for other avascular tissues, suffice.[137] Diffusion mechanisms apparently remain adequate as long as the wall remains below a certain critical thickness, and the development of a vascular plexus in the inner portion of the wall may constitute a response to progressive thickening from any cause.

As intramural plexuses develop, hemorrhage and other degenerative changes take place within the parent vascular wall.[137] These changes are accounted for on the basis that the main tensile strength of the vessel is determined in large part by the tough inelastic adventitia. It might be added that calcification of the vessel wall would have a similar effect. Increasing pressure within the lumen causes a compression of the intima and media between this force and the outer coat, with resulting compression of the intramural blood supply. Wherever in the body hemorrhage undergoes organization, there is a tendency to liberate cholesterol. This is to be seriously considered as one possible mechanism for the local deposition of cholesterol in intimal plaques.

As we have noted previously, a universal reaction, most likely caused by hemodynamic factors acting over long periods, is a progressive thickening of the intima. It is now evident that the intima, probably avascular originally, develops progressively a network of capillaries.[139,140,49,78] Probably this is an adaptive device to supply the extranutritional demands of the thickened intima through which diffusion no longer suffices. But this adaptive device is not without its penalties, for intramural hemorrhages may occur in the region of such plexuses of capillaries, perhaps by the mechanism suggested by Winternitz. The disruption of tissues by this complication evidently results in the liberation of thromboplastin and, with the slowing of the blood stream by the plaque in which it exists, thrombi may form. This may be relatively trivial, in which case the thrombus may be organized and incorporated into the plaque, or it may completely occlude the lumen. Paterson points out that the frequency of this event in any series of coronary thrombi depends entirely upon the pains which are taken in searching for them.[139] In his own series, he found intramural hemorrhage in 89 per cent of cases and Nelson reported an incidence of 90 per cent.[141] In this regard, Ogilvie aptly remarks, "vascularization of the intima initiates a vicious circle whereby hemorrhage stimulates repair and repair predisposes to hemorrhage."[142] Such intramural hemorrhages may have a third major effect—the initiation of widespread nervous reflexes with the production of vasomotor collapse and sudden

death.[143] Fresh intramural hemorrhages are almost always present in cases of coronary arteriosclerosis, while they are absent in individuals who die from obvious extracardiac disease.

One of the enigmas of the experimentally produced atherosclerotic plaque is that it does not result in the complication of thrombosis. This may be owing to the fact that small mammals and even dogs seem to lack mechanisms for the development of intramural plexuses of vessels. Since their vessel walls are considerably thinner than those of man, it may be that diffusion mechanisms suffice for a relatively longer period than in the human being, and hemodynamic considerations may be such that the stimulus for progressive thickening of the intima is also less. If this is true, then hemodynamic factors in the human being assume considerably greater importance than has heretofore been attributed to them.

Comment

In the past, the definitive characteristics of arteriosclerosis have been based chiefly on microscopic structural changes and from those have been drawn inferences as to etiology. This is a proper procedure insofar as it might permit comparisons of experimentally produced lesions with the spontaneous human variety. However, as we have said, when lesions are in an advanced or end-stage, inferences as to etiology are difficult, if not impossible, because of the limited range of response of which the various tissue components of the arterial wall are capable. It should be emphasized that whatever inferences are attempted, the response of the total wall should be taken into account.

The most easily recognized changes occur in the intima, and, for this reason, alterations in this particular layer have received considerably more emphasis than those in the other strata, particularly by the proponents of the lipid-metabolic theory. It may be concluded that intimal changes seldom occur alone, nor can they be considered as occurring prior to less pronounced structural alterations elsewhere in the vascular wall. The fundamental intimal change is a proliferative one. If undisturbed by secondary degenerative changes,[113-115] various intimal components are capable of construction of a tissue which resembles that of the subjacent vascular wall.

In the human subject, a similar series of events occurs in the process of recanalization of a thrombosed vessel. Thus the reaction may be regarded primarily as a reparative one. The various potentials displayed in this process consist of the proliferation and orientation of fibroblasts, probably originating from scattered undifferentiated mesenchymal cells, which lie between endothelium and internal elastic lamella as a basic tissue component of arteries of the newborn child. Following orientation of fibroblasts, there is a deposition of collagen between them, a new formation of elastic fibers, and even a differentiation of fibroblasts into smooth muscle cells.

As Hass points out, "seldom does this response proceed to perfect vascular reconstruction."[2] In most instances, the fibrous elements are predominant and secondary degenerative changes in the form of mucoid, hyaline, or lipid deposits appear along with macrophages and even inflammatory reaction. Generally, deposition of calcium is also considered in this category, although, from our own studies,[3-9] it appears that the latter is centered about degenerative changes in the elastic fiber, except in the media in which degenerative changes of muscle may also proceed to calcification.

The resistance of the various structural components of the artery wall varies to some extent with the injurious agent. Thus the endothelium is the component which appears to be most sensitive to ionizing irradiation, while smooth

muscle and connective tissue structures are less so.[109] Nevertheless, it has been shown that elastic membranes may also be damaged by irradiation and undergo changes similar to those in physiologic aging.[144] Injury by heat and cold may destroy all of the cellular elements while leaving the elastic framework damaged but intact. Although the elastic membrane may for some time resist pressures considerably higher than those likely to occur in the human subject, direct mechanical trauma may be capable of causing breaks in elastic membrane without producing any apparent injury to other components of the vessel wall. In a study of aortic transplants in dogs, it was observed that in grafts stored less than forty days, up to 50 per cent of the muscle of the media survived, while none survived in grafts stored over forty days, although the elastic tissue survived.[145] Certain hormones, such as norepinephrine alone or in combination with thyroxine, are capable of producing degenerative changes in muscle leading to necrosis and decalcification, while others, such as female sex hormones, may produce a pronounced hypertrophy of muscle and a proliferation of elastic fibers.

The various vascular components appear to be interdependent insofar as resistance to injury. The elastic structures seem to be most protective. Ssolowjew showed that the course of the arterial lesion depends upon the degree of injury to the elastic framework.[131] Among other things, he noted that isolated transverse lacerations of the elastic lamellae of the inner media rendered the overlying intima more permeable to substances circulating in the blood, such as trypan blue and cholesterol.

Finally, the intramural vascular response of the arterial wall to injury is most interesting and important. At least in the human being, this appears to be in the nature of an expression of vascular adjustment.[137] Such a conclusion seems justified since this response is lacking in those vessels which remain sufficiently thin throughout life so that diffusion from the endothelium can provide sufficient nutrition. This observation deserves reemphasis since those mammals generally utilized in the experimental production of atherosclerotic lesions appear to lack the potentialities for this response. Thrombosis and hemorrhage may represent complications of this response which may explain the lack of such complications in the experimental animal.[139]

This presentation, therefore, serves to emphasize the fact that the arteriosclerotic process, from whatever cause, involves not only the total wall but the development of such structures as intramural vascular components and the formation of elastic and muscle fibers in areas in which they were not present initially. It is in the light of these various reactions that we shall evaluate the three major concepts of the etiology of arteriosclerosis in a following report.

From the Departments of Pathology, The Jewish Hospital and St. Louis University School of Medicine, St. Louis, Missouri. *The investigations of the author cited in this report were supported in part by Research Grant H-1514 from the Department of Health, Education, and Welfare of the National Institutes of Health, U. S. Public Health Service, and in part by grants from the David May-Florence G. May and Louis Monheimer Research Funds of the Jewish Hospital, St. Louis, Missouri.*

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D. B. BRUSCA: Use of silicone spray on the skin of bedridden patients. New York J. Med. 56: 894-895, 1956.

A DIET low in fat, high in protein, and moderate in carbohydrates was found to be beneficial for elderly patients. Adequate meals, sunlight, and indoor or outdoor recreation are better than vitamin therapy in restoring older people to useful living.

Decubitus ulcers, habitual incontinence, and bone demineralization can be improved or cured by high protein and mineral intake. Bed exercises and gradual ambulation help bedridden patients assimilate the necessary foods. Older patients enjoy fruits cooked, baked, or in pastry, and milk and milk products.

M. B. FERDERBER: The role of nutrition in geriatric restoration. Pennsylvania M. J. 58: 697-699, 1955.

Editorial

The social contribution of old age*

We live in a work-centered society. The "die in the harness" philosophy is dominant rather than the "dolce far niente" philosophy of the Italians and other southern Europeans. The expression that "it is better to wear out than to rust out" is still common, although there is no medical evidence to substantiate the belief that persons who retire are not as healthy and do not live as long as those who continue to work. This guilt feeling toward leisure in the later years may be left over from pioneer days when unremitting toil by old and young was necessary to maintain life.

Some day this guilt feeling toward leisure in the later years may disappear just as it has disappeared in the case of the shorter work day and long weekend. But, as of the present time, we must recognize that a complete solution of the problem of economic old age requires not only reasonable economic security, but opportunity for older persons to continue working if they are able and desirous of doing so and opportunity for them to function as useful and welcome members of the community . . .

With due respect for the poet and his vision of slippered ease, it seems to me of paramount importance that both older persons and the community at large come to realize the unique social contribution that older persons can make. They alone have had a life-time of experience on which to draw and are released from some of the daily demands upon time and energy which prevent younger people from achieving perspective and developing an interest in community welfare. They are in the best position to appreciate how vital the community's well-being is to the well-being of the individual and family, and how vital the constant improvement in our social order is to the well-being of oncoming generations. In short, they have far greater potentialities to be socially creative than younger persons, if only they and the community fully realized it. Let us hope, not only for the sake of older persons themselves, but for the sake of the common good, that we in the United States will come to appreciate more and more the precious asset we have in the older generation.

Arthur J. Altmeyer, Ph.D., LL.D.
Madison, Wisconsin

**Excerpts from an address given at Cornell University, Ithaca, New York, December 15, 1955.*

Federal-state conference on aging

Representatives appointed by the governors of 41 states and of Hawaii and Puerto Rico met June 5 to 7 in Washington with various officials of the federal government for a national Conference on Aging. The Conference was jointly sponsored by the newly established Federal Council on Aging and the Council of State Governments. Its

purpose was to explore the area of government responsibility in the field of aging and to lay the groundwork for closer cooperation between the states and the federal government.

The principal speakers included Frank Bane, executive director, Council of State Government; Robert B. Meyner, governor of New Jersey; Arthur Larson, under secretary of the Department of Labor; and Marion B. Folsom, secretary of the Department of Health, Education, and Welfare. The White House was represented in an address of welcome by the Hon. Howard Pyle, deputy assistant to the President. Panel participants and group discussion leaders were drawn from some of the top experts in the field.

In general, the Conference avoided the discussion of program content as such, and concentrated on how the federal and state governments could work together to expand, and give better direction to, the various programs now in existence. The six discussion groups came up with a total of some 50 specific recommendations on how these objectives could be achieved. Although no floor votes were taken, the majority of the delegates seemed to be in substantial agreement with the proposals advanced.

One important recommendation urged that each state set up an interdepartmental committee or a citizens' committee, or a combination of the two, to coordinate and promote facilities for the aging. "Vital to the success of any such action," the recommendation read, "would be the direct involvement of the governor, either personally or through the appointment of a special assistant." The procedure followed in California and New York was given as an example of progress made by using such an approach. It was also recommended that the Federal Council on Aging and the Council of State Governments create a joint committee of the two agencies as an additional facility for communication and cooperative consultation.

The Federal Council on Aging, representing a dozen governmental departments or agencies which have programs relating to aging, was established last April by President Eisenhower. Its chairman is Roswell B. Perkins, assistant secretary of the Department of Health, Education, and Welfare and the Conference was the first major project undertaken.

The Council of State Governments has, in the last year or two, shown increasing interest in aging. In June 1955 it issued a report entitled "The States and Their Older Citizens" which constitutes a notable summary of the problem and a program of action.

A full report of the Conference will be published and will be available at a later date.

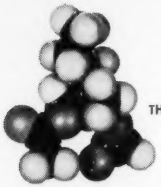
MERRILL ROGERS
Washington, D. C.

Hypertension in Northern Japan

NILS P. LARSEN, of Honolulu, writes me that he has just returned from a month in the Orient where he gave a paper on planned parenthood. The thinking people in Japan are desperate because they have on their rocky islands 89 million people, with food for only some 35 million. The situation is bad enough as it is; it can easily get much worse.

Dr. Larsen said he had a most interesting discussion with Dr. Watanabe concerning the frequency of cerebral hemorrhage. The Japanese in the North Island are highly subject to hypertension. Their pressures average considerably higher than do those of persons living in the southern islands. In a certain fishing village in northern Japan, where everyone eats salted fish and salted food, almost every person over 40 has high blood pressure. Curiously, in spite of this, coronary thrombosis is infrequent among the Japanese.

WALTER C. ALVAREZ, M.D.



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Digests
FROM CURRENT LITERATURE

Histaminic Cephalalgia

B. T. HORTON. J.A.M.A. 160: 468-469, 1956.

Ninety per cent of patients with histaminic cephalalgia are men over 40 years of age.

The condition is characterized by a unilateral headache generally lasting less than an hour. The headache tends to awaken the patient at night one to two hours after he has gone to sleep, and the severity of the pain makes the patient get out of bed and pace the floor. At the height of the pain, there is watering and congestion of the eye, rhinorrhea or stuffiness of the nostril, sweating, and often, visible dilatation of the temporal vessels of the involved side of the head.

A constant, excruciating, burning, and boring pain is the outstanding complaint. The development of a Horner's syndrome is not uncommon and may disappear after a given series of attacks have ceased, or may remain permanently.

The subcutaneous administration of 0.35 mg. of histamine base will precipitate an attack of histaminic cephalalgia; so will alcohol. An induced attack usually can be aborted promptly by the intravenous administration of 1 cc. dihydroergotamine.

Histaminic cephalalgia represents a localized anaphylactoid reaction, with both localized and systemic manifestations. During spontaneous and induced attacks, histamine is released from the shocked tissues in the region of the pain and accounts for most local phenomena.

The object of treatment is twofold: (1) to alleviate the pain of an acute attack and (2) to prevent subsequent attacks. The intravenous administration of 1 cc. of dihydroergotamine combined with the inhalation of 100 per cent oxygen will abort an acute attack in one to five minutes. A rectal suppository containing 2 mg. of ergotamine tartrate and 100 mg. of caffeine, if used at bedtime, with or without a sedative, will often prevent nocturnal attacks. Histamine desensitization is the treatment of choice for preventing further attacks.

Histamine is a most potent therapeutic agent, giving complete relief to more than 90 per cent of patients with histaminic cephalalgia.

Geriatric Patients in a Mental Hospital

F. H. ERNST, JR., W. A. OLIVER, A. SIMON, and N. MALAMUD. California Med. 84: 172-175, 1956.

Certain crises lead to institutionalization of the aged. These include assaultiveness, suicidal attempts, delusions or hallucinations, defective judgment in the management of self or resources, and inappropriate sexual behavior. Some patients without overt indications of psychosis are committed to mental hospitals solely because of confusion or wandering tendencies, irritable and noisy behavior, and, in rare instances, symptoms of alcoholism.

Study reveals that, of 100 patients with the organic brain syndrome, 44 need the facilities and care offered by state institutions. Nineteen need the diagnostic facilities of the institution but, after diagnostic procedures, are suitable candidates for other types of care. The remainder of patients can be cared for in nursing homes, private hospitals, or at home.

Emotional factors are often coincident with onset of the chronic brain syndrome. Eighty-eight per cent undergo significant emotional stress preceding onset of mental symptoms.

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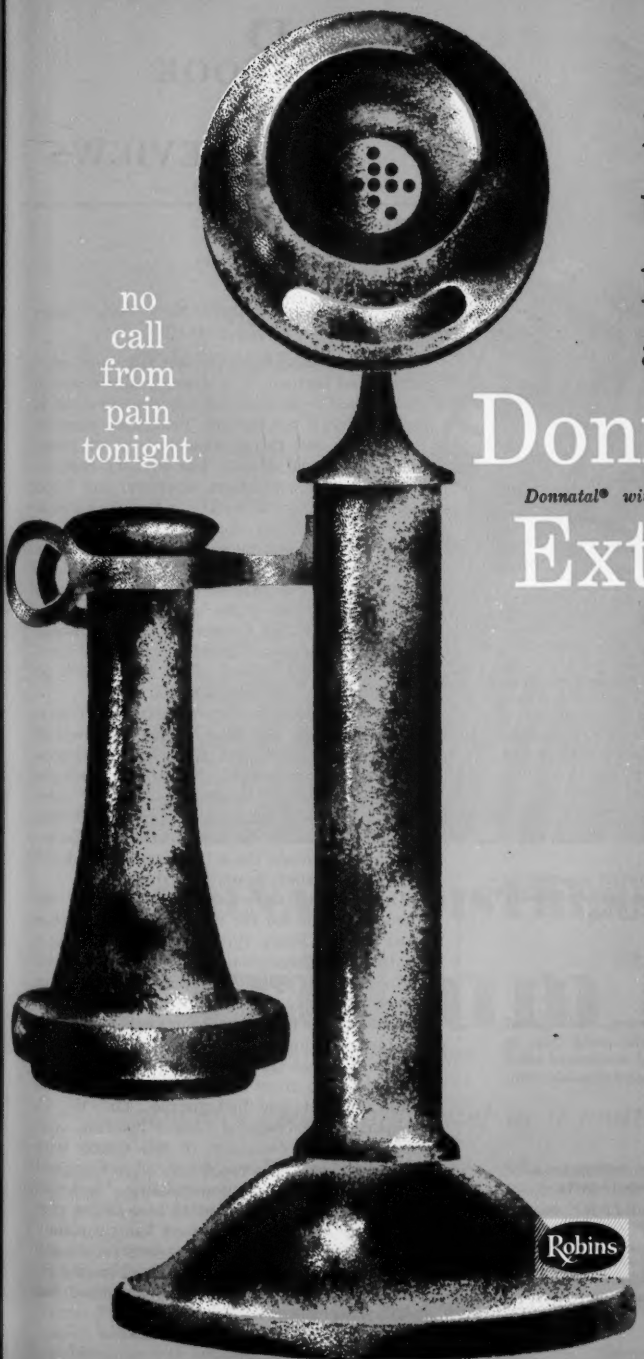

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Hyoscyamine Sulfate	0.3111 mg.
Atropine Sulfate	0.0582 mg.
Hyoscine Hydrobromide	0.0195 mg.
Phenobarbital (¼ gr.)	48.6 mg.

1. Goodman, L. S., and Gilman, A.: The Pharmacologic Basis of Therapeutics, N. Y., The Macmillan Co., 1955; p. 127.

Robins

A. H. ROBINS CO., INC.
RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit Since 1878

*TM Reg. U. S. Pat. Off.—pat. applied for

It's easy
to make
appetizing,
high-protein
foods and drinks
with

GEVRAL* PROTEIN

Geriatric Vitamin-Mineral-Protein Supplement

GEVRAL PROTEIN is a dry powder containing 60% protein and 26 important vitamins and minerals. Because it is virtually tasteless, it can be utilized in many kinds of dishes and drinks. It can be sprinkled on dry foods, mixed with others, or dissolved in liquids. The easy-to-make recipes below suggest some of the ways this outstanding supplement can be utilized in the high-protein diet.

***high-protein* HOT COCOA**

1 heaping tbsp. GEVRAL PROTEIN
1 heaping tsp. cocoa powder
hot water

Put cocoa powder and GEVRAL PROTEIN together in teacup. Add *small* amount of water to make smooth paste. Stir in additional water to fill cup.

***high-protein* SOUP**

1 heaping tbsp. GEVRAL PROTEIN
½ can condensed soup
¾ cup water

Put GEVRAL PROTEIN in saucepan. Add *small* amount of water to make smooth paste. Stir in remaining water, then slowly add condensed soup —chicken, asparagus, celery, or cream of mushroom.

***high-protein* HOT CEREAL**

1 heaping tbsp. GEVRAL PROTEIN
½ cup any hot cereal

Mix GEVRAL PROTEIN with cereal during or after cooking. Add sugar, milk, or cream to taste.

For additional information and other recipes, ask your Lederle representative.

LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

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BOOK REVIEWS

Smoking and Cancer
A Doctor's Report

ALTON OCHSNER, M.D., 1954. New York: Julian Messner, Inc. 86 pages. $2.00.

This little monograph, written for both physicians and laymen, is a strongly documented, impassioned indictment of tobacco smoking as the primary, if not the sole, provoking cause of pulmonary and throat cancers and of much coronary arterial disease. The author's zeal, intense personal conviction, sincerity, and blind faith in the statistical method as proof of causation are more than apparent; they are conspicuous. Less conspicuous, especially to the layman, is the significant omission of consideration of etiologic factors other than tobacco smoke. Only three pages of text are given to the chapter "Other Causes of Lung Cancer," and these are devoted largely to skeptical comments anent the validity of all data which do not confirm Dr. Ochsner's thesis.

When prejudice replaces objectivity, discussion becomes an argument. When only part of the truth is revealed and part withheld, science is violated. When violent emotions displace the calm of judgment, conclusions become questionable. One is reminded of the ancient Chinese proverb: "He who raises his voice in a discussion thereby admits the exhaustion of his ideas." And Dr. Ochsner shouts his exhortations.

The opening sentences of page 1 set the theme and tone for the whole text: "Cigarettes cause cancer. Every type of smoking carries a deadly risk. Tobacco is a loaded, often lethal, weapon. Time pulls the trigger." This is not objective science.

. Here is not the place to review the whole complex question of the etiology of pulmonary or other cancers. But data, pointing their fingers of suspicion to many other factors than tobacco smoke, should not be ignored. Dr. W. C. Hueper, of the National Cancer Institute, concludes a recent discussion of this matter with the following well-considered, objective, and scientifically sound recommendation: "It would be most unwise at this time to base future preventive measures of lung-cancer hazards mainly on the cigarette theory, and to concentrate the immediate epidemiological and experimental efforts on this evidently over-propagandized and insufficiently documented concept."

(Continued on page 42A)

in URINARY DISTRESS

Pyridium®

(Brand of Phenylazo-diamino-pyridine HCl)

provides gratifying relief in a matter of minutes

Painful symptoms impel the patient with acute or chronic pyelonephritis, cystitis, urethritis or prostatitis to seek your aid. In the interval before antibiotics, sulfonamides or other antibacterial measures can become effective, the nontoxic, compatible, analgesic action of PYRIDIUM brings prompt relief from urgency, frequency, dysuria, nocturia or spasm. At the same time, PYRIDIUM imparts an orange-red color to the urine which reassures the patient. Used alone or in combination with antibacterial agents, PYRIDIUM may be readily adjusted to each patient by individualized dosage of the total therapy.

SUPPLIED: In 0.1 Gm. (1½ gr.) tablets in vials of 12 and bottles of 50, 500, and 1,000.

PYRIDIUM is the registered trade-mark of Nepera Chemical Co., Inc., for its brand of phenylazo-diamino-pyridine HCl. Sharp & Dohme, Division of Merck & Co., Inc., sole distributor in the United States.

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Philadelphia 1, Pa.
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"MEDIATRIC"

CAN EXPECT

A HEALTHIER,

HAPPIER

"SECOND FORTY

YEARS"

Steroid-Nutritional Therapy

Provides a

Constructive Approach

in Preventive Geriatrics

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AYERST LABORATORIES

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Book Reviews

(Continued from page 40A)

This book will appeal to those who believe as Dr. Ochsner believes. It will leave cold those who seek to know the whole of truth. Whether physicians should recommend this book to their tobacco-addicted patients, or avoid the hazard of serious iatrogenic psychosomatic illness by disapprobation, depends upon their own personal opinion. However, no matter what their own personal attitude may be, it is urgent that doctors should themselves read the book before recommending it to any layman.

EDWARD J. STIEGLITZ, M.D.
Washington, D. C.

A Textbook of Medicine

RUSSELL L. CECIL, M.D., and ROBERT F. LOEB, M.D., editors, 1955. Philadelphia: W. B. Saunders Company. Ninth edition, illustrated, 1,786 pages. $15.00.

This new edition of the famous textbook of medicine by Cecil and Loeb has been greatly expanded with new material in order to keep abreast of the recent advances in internal medicine. Not only has most of the material been thoroughly revised and brought up to date, but some 44 new discussions have been added. Three exceptionally competent New York clinicians served as associate editors: Doctors Alexander B. Gutman, Walsh McDermott, and Harold G. Wolff.

The format, printing, binding, and indexing of the cyclopedic work are excellent. In view of the fact that it is primarily intended as a text for medical students, the illustrations are only fair. To the reviewer they are inadequate in number, too often represent extreme examples of the disease under consideration, and are occasionally not too well reproduced. However, it is recognized that more illustrations would add considerably to the bulk and cost of the book.

There is no need to comment on the accuracy and comprehensiveness of this work. Although much of the material has been revised, there is also considerable reprinting of former contributions without revision. This is notable in those originally prepared by contributors who have died as long as eighteen to twenty-four months prior to the publication of this edition. The words geriatrics, age, and old do not appear in the index; senescence, senescent, and senile do appear in connection with a few more or less specific disorders, such as arteriosclerosis, osteoporosis, psychoses and in one new article on senile heart disease. The effects of aging upon the etiology, character, course, prognosis, and therapy of the many disorders discussed are largely ignored.

EDWARD J. STIEGLITZ, M.D.
Washington, D. C.

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Peptonized iron is virtually predigested. It is absorbed as well as ferrous sulfate, and is one-tenth as irritating to the gastric mucosa. Anemias refractory to other forms of iron will often respond promptly to Livitamin therapy.

The Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} (crystalline)	20 mcg.
Niacinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

New York Kansas City San Francisco

for assured

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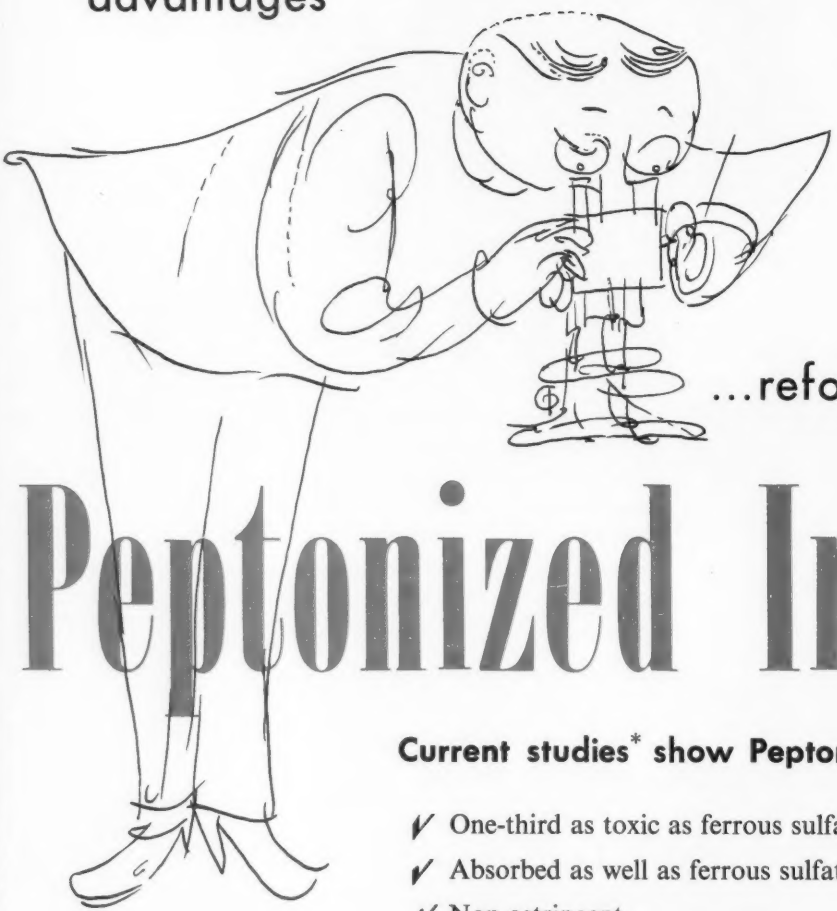

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Peptonized Iron

Current studies* show Peptonized Iron

- ✓ One-third as toxic as ferrous sulfate.
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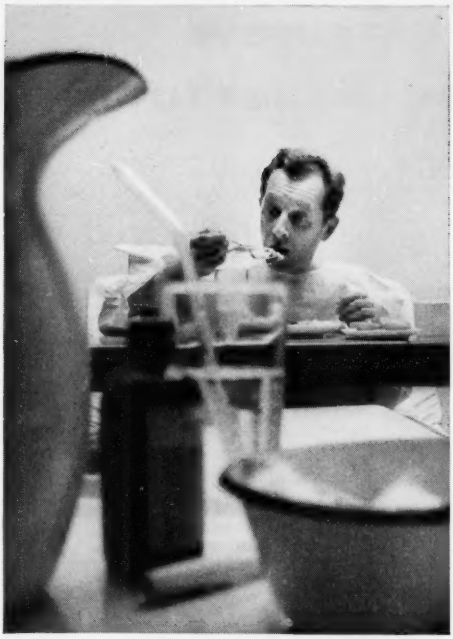
- ✓ Free from tendencies to disturb digestion. (*One-tenth as irritating to the gastric mucosa as ferrous sulfate.*)
- ✓ More effective in iron-deficient anemias.

LIVITAMIN® with Peptonized Iron

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Read before the American Association for the Advancement of Science, Zoological Section, Atlanta, Georgia, December, 1955.

THE S. E. MASSENGILL COMPANY Bristol, Tennessee — New York — Kansas City — San Fr



how you can shorten convalescence in adults

While 'Trophite' was developed to increase appetite in below-par children—and thus increase growth—it has also proved extremely useful in convalescent adults.

That is because 'Trophite' not only improves appetite but also promotes the proper utilization of food. Studies with B_{12} emphasize "the importance of adequate supplies of this vitamin in the metabolism of carbohydrate and fat, including not only the conversion of carbohydrate to fat, but the metabolism of fat itself." (Editorial, J.A.M.A. *153*:960)

In addition to B_{12}, 'Trophite' contains B_1 whose value in combating anorexia is established. Try 'Trophite' in your next convalescent —and see how quickly he is up and about. 'Trophite' is available both as tablets and as a truly delicious liquid. Each tablet or teaspoonful (5 cc.) supplies: 25 mcg. B_{12}, 10 mg. B_1.

the high potency combination of B_{12} and B_1

Trophite* *for* appetite

*T.M. Reg. U.S. Pat. Off. *Smith, Kline & French Laboratories, Philadelphia*

a new
mental clarifier for the aged...

for safe, effective treatment of moderately disturbed aged patients...

Senilex
"DURST"

Today's increasing life span has increased the number of aged patients for every physician so greatly that geriatrics has become a part of his everyday practice. This is especially true in considering changes in the central nervous system, which frequently mean treatment in modern private or public mental hospitals. But a still greater number of the aged are subject to only mild memory defects or slight confusion resulting in some abnormal behavior. These cases may be treated at home . . . and clinical tests prove that SENILEX has shown remarkable results in these states.

SENILEX is a safe, simple regimen for moderately disturbed patients. Used on ambulatory basis for rehabilitation of the aged without institutionalization. There are no specific contraindications. Prescribe SENILEX for your next case.

INDICATIONS: Senile Mental Deterioration, Especially Mild Memory Defects, Confusion and Abnormal Behavior.

ACTION: Produces both objective and subjective physical improvements, marked behavior improvement, better performance on psychological testing, and increase in intelligence quotient. Restores normal blood lactic acid values and produces more normal electroencephalographic tracings.

DOSAGE: 2 tablets 3 times daily. Lower dosages for maintenance after maximum effect is reached.

SUPPLIED: Furnished in bottles of 96 tablets.

FORMULA:

Pentylenetetrazol	100 mg.
Niacin	50 mg.

Send for literature and samples

More than 25 years of service to the Medical Profession.

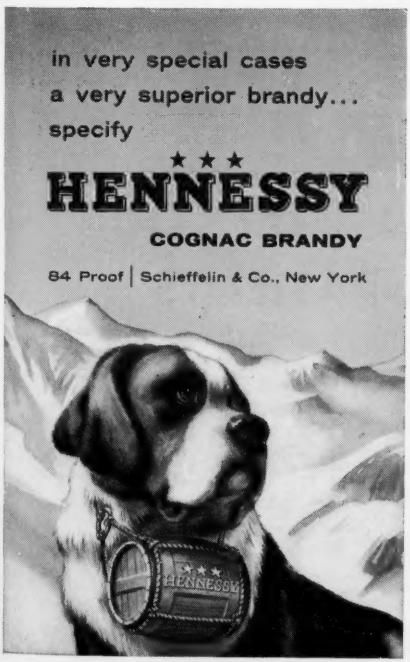
S. F. DURST & COMPANY, INC., *Phila. 20, Pa.*

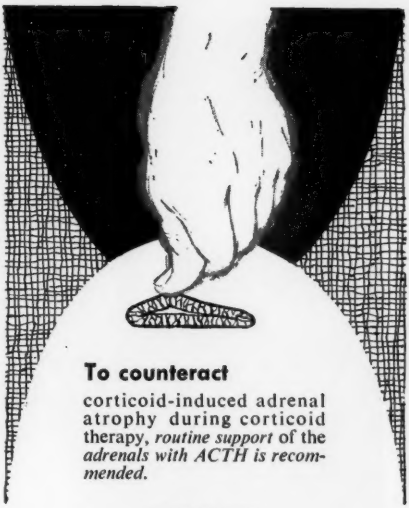
Activities and Announcements . . .

Coming Meetings

The first *Pan American Gerontological Congress* will be held in Mexico City, September 15 to 22, 1956, with Dr. Manuel Payno, president of the Sociedad Mexicana de Geriatria as presiding officer. Dr. E. V. Cowdry of Washington University is chairman of the North American Committee of Cooperation. There will be two simultaneous sessions of the Congress on (1) Medical and Biologic Aspects and (2) Social and Economic Aspects. Travel and hotel reservations may be made through Mrs. V. Kelly, Division of Cancer Research, Washington University, 660 S. Kingshighway Boulevard, St. Louis 10, Missouri.

The *Ninth Annual Scientific Meeting of the Gerontological Society, Inc.*, will be held at Hotel Hamilton, Chicago, Illinois, November 8 through 10, 1956. Dr. Edward J. Stieglitz, 1726 Eye Street, N.W., Washington 6, D. C., is program chairman. "Preparation for Senescence" will be the principal theme of the meeting and there will be a symposium on "Education for Maturity."





To counteract
corticoid-induced adrenal atrophy during corticoid therapy, *routine support* of the *adrenals with ACTH is recommended.*

THIS IS THE PROTECTIVE DOSAGE RECOMMENDATION FOR COMBINED CORTICOID-ACTH THERAPY

- When using *prednisone* or *prednisolone:* for every 100 mg. given, inject approximately 100 to 120 units of HP* ACTHAR *Gel.*
- When using *hydrocortisone:* for every 200 to 300 mg. given, inject approximately 100 units of HP* ACTHAR *Gel.*
- When using *cortisone:* for every 400 mg. given, inject approximately 100 units of HP*ACTHAR *Gel.*

Discontinue administration of corticoids on the day of the HP*ACTHAR *Gel* injection.

HP*ACTHAR® *Gel*
(IN GELATIN)
The Armour Laboratories brand of purified adrenocorticotropic hormone—corticotropin (ACTH)
*Highly Purified

Unsurpassed in Safety and Efficacy
More than 42,000,000 doses of ACTH have been given

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TEMPTING MENUS FOR YOUR SPECIAL DIET PATIENTS

Doctors find their special diet patients are actually tempted by meals when Beech-Nut Strained and Junior Foods make up the menu. No complaints about mealtime monotony, because Beech-Nut has unlimited food combinations. Here, in convenient, economical form, are tasty vegetable-meat dishes, soup varieties and healthful vegetables. Along with the "just picked" flavor, they are rich in vitamins and minerals. No wonder doctors find patients enjoy dietary meals that include Beech-Nut Strained and Junior Foods.

28 STRAINED FOODS
27 JUNIOR FOODS

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PARKINSONISM

Artane*

HYDROCHLORIDE

Trihexyphenidyl HCl *Lederle*

effective over long periods

ARTANE is a strong antispasmodic, effective in all three types of Parkinsonism—Postencephalitic, Arteriosclerotic, and Idiopathic. Unlike certain other such drugs, it does not lose effectiveness when given over long periods. It is usually well tolerated, and has no deleterious effect on bone marrow function.

ARTANE is supplied in 2 mg. and 5 mg. tablets, and as an elixir containing 2 mg. per teaspoonful (4 cc.) Dosage: 1 mg. the first day, gradually increased, according to response, to 6 mg. to 10 mg. daily.

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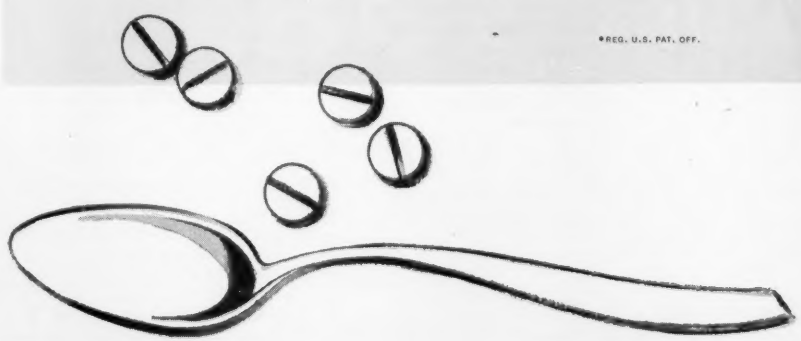


Back to first principles for REAL BREAD

The makers of Pepperidge Farm Bread believe in fresh natural ingredients for nutritionally valuable and taste-pleasing bread.

So the flour for our Whole Wheat Bread is stone-ground in our own grist mills—contains the wheat germ and all the natural goodness of the whole grain. And we use whole milk, sweet cream butter, yeast and unsulphured molasses to make our bread.

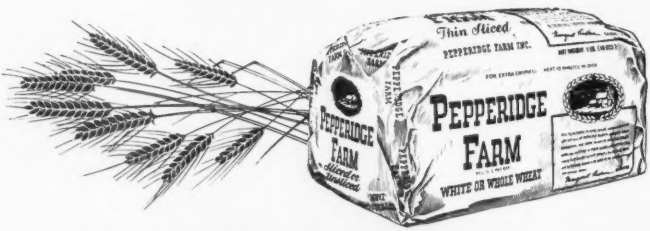
We offer White Bread, too—made with *unbleached* flour, dairy-fresh ingredients.

We suggest that Pepperidge Farm Bread deserves a place on your table.

For information about our special SALT-FREE Bread, please write to me.

Margaret Rudkin

DIRECTOR



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Private Beach, Pools, Sports, special supervised Children's Playtown . . . dining rooms, cafeteria, cocktail lounges, entertainment.

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MENIC™

alleviates
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MENIC combining the analeptic, pentylenetetrazole, with the cerebral vasodilator, nicotinic acid, is *"...safe and simple...practical and inexpensive... can be used without hesitation on an ambulatory basis...especially useful in combating symptoms of abnormal behavior..."*[1]

[1]Levy, S.: J.A.M.A., 153:1260-1265, 1953.

Each scored tablet contains pentylenetetrazole 100 mg. (1½ gr.), nicotinic acid 50 mg. (⅚ gr.). In bottles of 100 and 500 tablets. Literature and samples available upon request.

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speed convalescence—

Saturation Dosage
of water-soluble vitamins B and C

ALLBEE® with C

The highest ascorbic acid content (250 mg.) of any water-soluble vitamin capsule

In each capsule:

Thiamine hydrochloride	15 mg.
Riboflavin	10 mg.
Calcium pantothenate	10 mg.
Nicotinamide	50 mg.
ASCORBIC ACID	250 mg.

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results are obtained with STERANE[1]—3 to 5 times more active than hydrocortisone or cortisone.

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capacity is greatly enhanced. "Relief of symptoms is more complete and maintained for longer periods with relatively small doses."[2]

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of minerals and fluids usually remains undisturbed. This proves "especially advantageous in those patients with cardiac failure requiring therapy . . ."[3]

in bronchial asthma

Sterane®

brand of prednisolone

Supplied: White, 5 mg. oral tablets, bottles of 20 and 100. Pink, 1 mg. oral tablets, bottles of 100. Both deep-scored.

1. Johnston, T. G., and Cazort, A. G.: J. Allergy 27:90, 1956. 2. Schwartz, E.: New York J. Med. 56:570, 1956. 3. Schiller, I. W., et al.: J. Allergy 27:96, 1956.

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Division, Chas. Pfizer & Co., Inc.
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Superficial skin complaints usually respond dramatically to TASHAN CREAM 'Roche'

Antiprurient, soothing, and healing—contains vitamins A, D, E, and *d*-Panthenol, in a cosmetically pleasing water-soluble base which fastidious patients will enjoy using. Hoffmann-La Roche Inc., Nutley, N. J.

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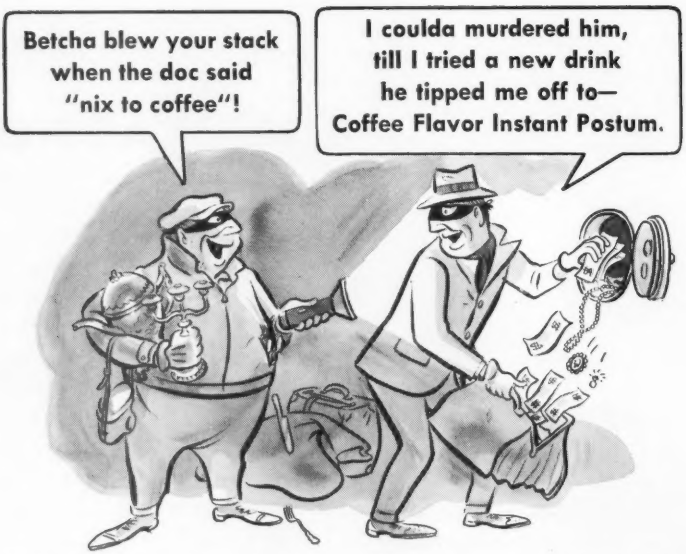
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I coulda murdered him, till I tried a new drink he tipped me off to— Coffee Flavor Instant Postum.

Coffee-loving patients usually resent being told to give up their favorite beverage. Why not suggest the caffein-free Instant Postums as coffee substitutes?

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Effective local treatment

FOR BEDSORES AND OTHER CHRONIC ULCERATIONS

May 15th. Severe decubitus ulcer over femoral greater tuberosity in a terminally ill patient.

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Routine application of White's Vitamin A & D Ointment promotes granulation and epithelization in *stubborn bedsores, chronic ulcers of varied etiology, burns and slow-healing wounds* that do not permit primary surgical closure. It is also useful as a protective and therapeutic covering in miscellaneous skin conditions characterized by abnormal dryness. White's Vitamin A & D Ointment provides vitamins A and D in a pleasant lanolin-petrolatum base that does not stain tissues or bed clothes.

℞ in 1½ oz. or 4 oz. tubes; 1 lb. or 5 lb. jars.

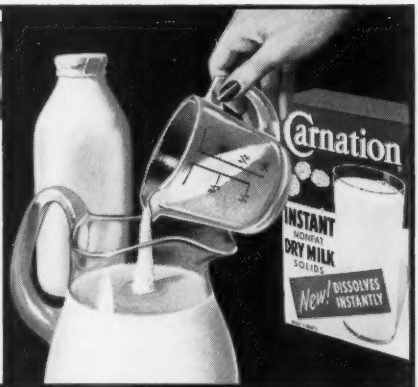
White's

WHITE LABORATORIES, INC., KENILWORTH, N. J.

July 12th. After 2 months of treatment with White's Vitamin A & D Ointment, ulcer crater reveals healthy granulation tissue

How CARNATION INSTANT provides new dietary advantages not possible with other forms of nonfat milk

Because Carnation Instant is a new *crystal form* of nonfat dry milk, the physician may specify a greater ratio of milk solids to water than supplied by bottled nonfat milk. The new crystal form may also be added to *whole* milk to increase its nutritive content.



WHEN LIQUIDS ARE RESTRICTED,

the physician may specify an additional heaping tablespoon of Carnation crystals per glass (or ⅓ cup additional crystals per quart.) This "self-enrichment" provides a 25% increase in protein, calcium and B-vitamins with no increase in liquid bulk.

25% "self-enriched" Carnation Instant also provides a more familiar heavier texture and richer flavor, well-liked by patients who are accustomed to drinking whole milk.

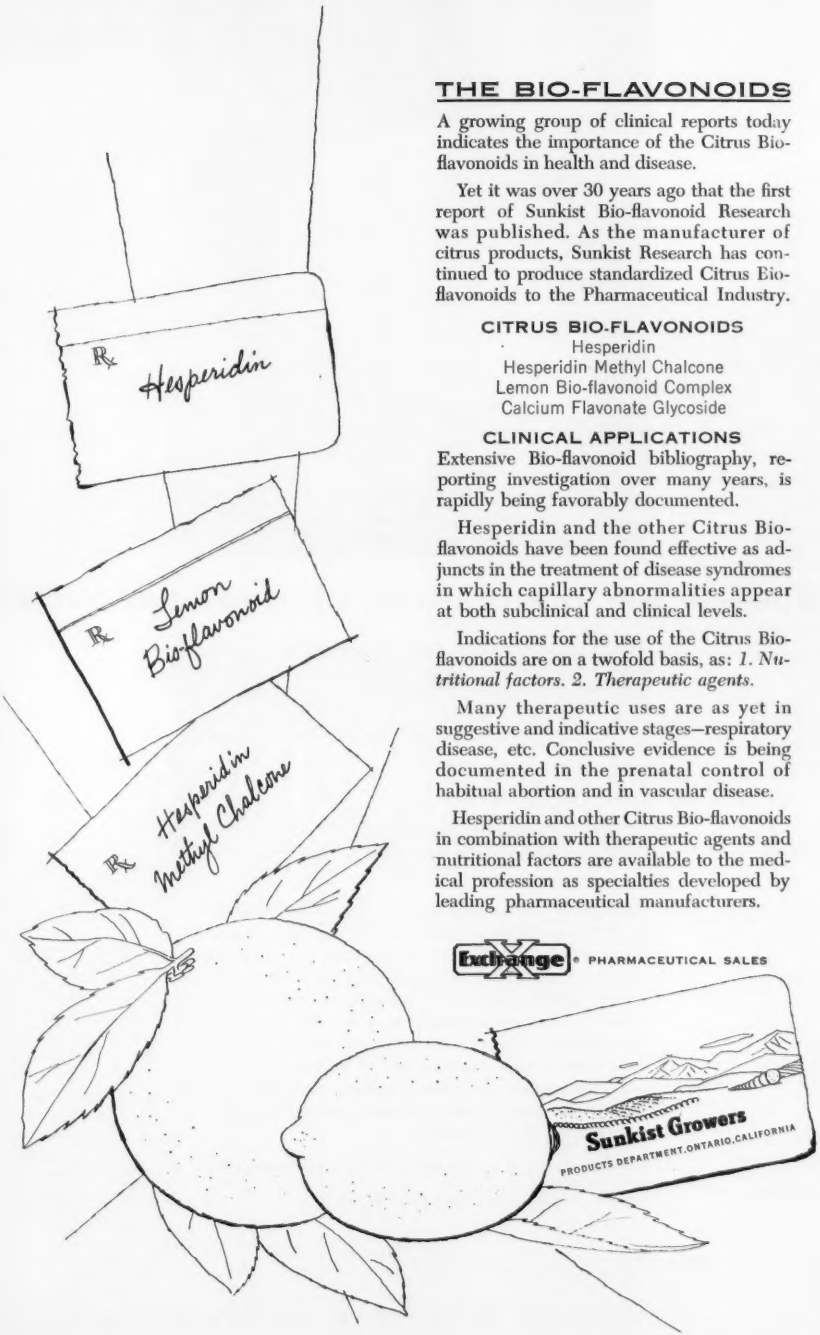
WHEN PROTEIN NEEDS ARE HIGH,

the physician may recommend the addition of 1⅓ cups Carnation crystals to each quart of *whole* milk. This *doubles* the protein, calcium and B-vitamin content.

The use of Carnation Instant in whole milk is of value when some fat is advisable but liquids should be restricted...and is also useful in increasing the protein in geriatric or convalescent diet without increasing fat or liquid bulk.

Other advantages of the Carnation exclusive Crystal Form

Fresh milk flavor, delicious for drinking.
Mixes instantly in ice-cold water.
Does not cake or harden in the package.
No special recipes needed.
Economical, available everywhere.



THE BIO-FLAVONOIDS

A growing group of clinical reports today indicates the importance of the Citrus Bio-flavonoids in health and disease.

Yet it was over 30 years ago that the first report of Sunkist Bio-flavonoid Research was published. As the manufacturer of citrus products, Sunkist Research has continued to produce standardized Citrus Bio-flavonoids to the Pharmaceutical Industry.

CITRUS BIO-FLAVONOIDS

Hesperidin
Hesperidin Methyl Chalcone
Lemon Bio-flavonoid Complex
Calcium Flavonate Glycoside

CLINICAL APPLICATIONS

Extensive Bio-flavonoid bibliography, reporting investigation over many years, is rapidly being favorably documented.

Hesperidin and the other Citrus Bio-flavonoids have been found effective as adjuncts in the treatment of disease syndromes in which capillary abnormalities appear at both subclinical and clinical levels.

Indications for the use of the Citrus Bio-flavonoids are on a twofold basis, as: *1. Nutritional factors. 2. Therapeutic agents.*

Many therapeutic uses are as yet in suggestive and indicative stages—respiratory disease, etc. Conclusive evidence is being documented in the prenatal control of habitual abortion and in vascular disease.

Hesperidin and other Citrus Bio-flavonoids in combination with therapeutic agents and nutritional factors are available to the medical profession as specialties developed by leading pharmaceutical manufacturers.

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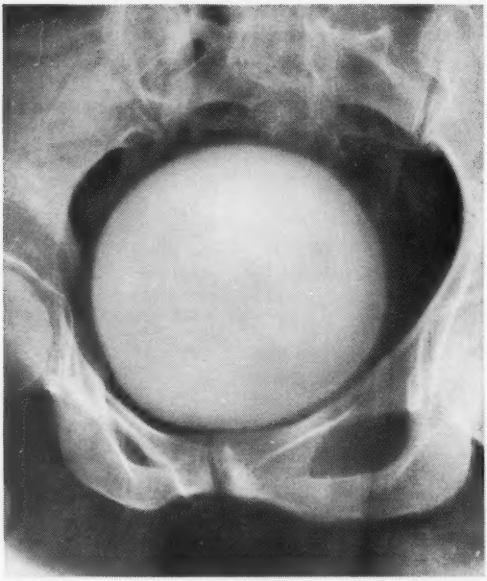

Relieves the postpartum bladder aseptically

URECHOLINE®

HYDROCHLORIDE

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URECHOLINE offers worthwhile therapeutic and psychologic advantages in managing urinary retention in the obstetrical patient. In one study[1] prophylactic administration of URECHOLINE Tablets to 129 postpartum patients reduced the incidence of urinary retention 80 per cent. Therapeutic use of the drug successfully relieved acute urinary retention in a large number of cases. All this can be achieved without the necessity for exposing the patient to the discomfort and risk of infection inherent in catheterization.

Supplied: 5 mg. and 10 mg. tablets, bottles of 100; 1-cc. ampuls, each containing 5 mg. of URECHOLINE Chloride.

Reference: 1. Fleming, A. R., Am. J. Obst. & Gyn., 64:134, 1956.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

The Protein Contribution of Oatmeal

Oats are richer in protein than other cereal grains commonly used for breakfast food purposes.[1]

Milled to retain all parts of the hulled oat kernel, rolled oats contain the protein of the germ and the outer seed layers as well as that of the inner cells.[3] Neither the commercial processing of oats nor the cooking of oatmeal in the home impairs the biologic value of the constituent protein.[3,4]

Experimental studies have established that the protein of oats is of higher biologic value than that of other grains.[5,6]

As eaten, the dish of oatmeal—1 ounce of oatmeal (weight before cooking) and 4 ounces of whole or skim milk—presents approximately equal amounts of oat protein and milk protein. This combined protein, readily applicable for all protein needs, supports excellent growth as well as tissue maintenance.[3,7]

IN GERIATRIC NUTRITION
In the problems of geriatric nutrition, of dealing with the self-imposed restrictions and distorted appetites of the aged, oatmeal offers definite advantages. It provides good protein, valuable vitamins and minerals, is low in sodium and purines, is easily eaten, readily digested, and promptly utilized.

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*Fuller, H. L., and Kassel, L. E.: METAMINE (triethanolamine trinitrate biphosphate) in Angina Pectoris, *J.A.M.A.*, *159*:1708-1713, December 31, 1955.

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Reference 1: Poumailloux, M., and Tetreau, H.: Official Report to Medicaments Trials Commission (France), 1949. Dailheu-Geoffroy: La Clinique, *46*:27, May 1951. Spuehler, O.: Schweiz. Med. Wochschr., *79*:518, 1949. J-F Merlen: Therapie, *6*:223, 1951. Palmer, J. H., and Ramsey, C.G.: Canad. M.A.J., *65*:16, July 1951; Current Med. Digest, *18*:94, October 1951. Fuller, H. L., and Kassel, L. E.: METAMINE (triethanolamine trinitrate biphosphate) in Angina Pectoris, J.A.M.A., *159*:1708-1713, December 31, 1955.

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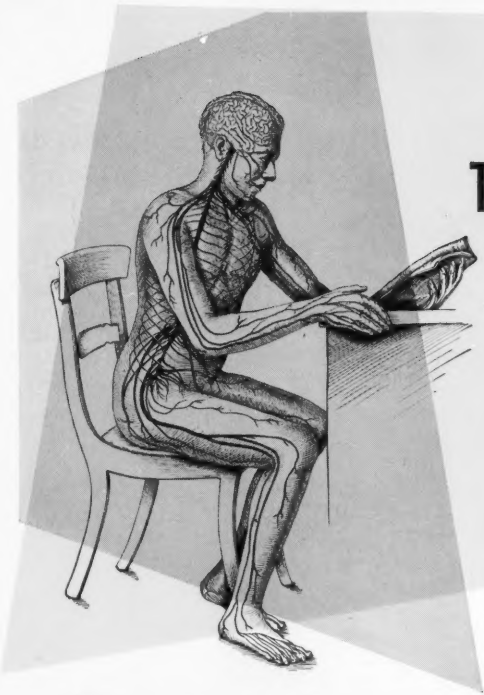

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*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, ed. 2, New York, The Blakiston Company, Inc., 1954, chap. 98, pp. 702, 703.

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